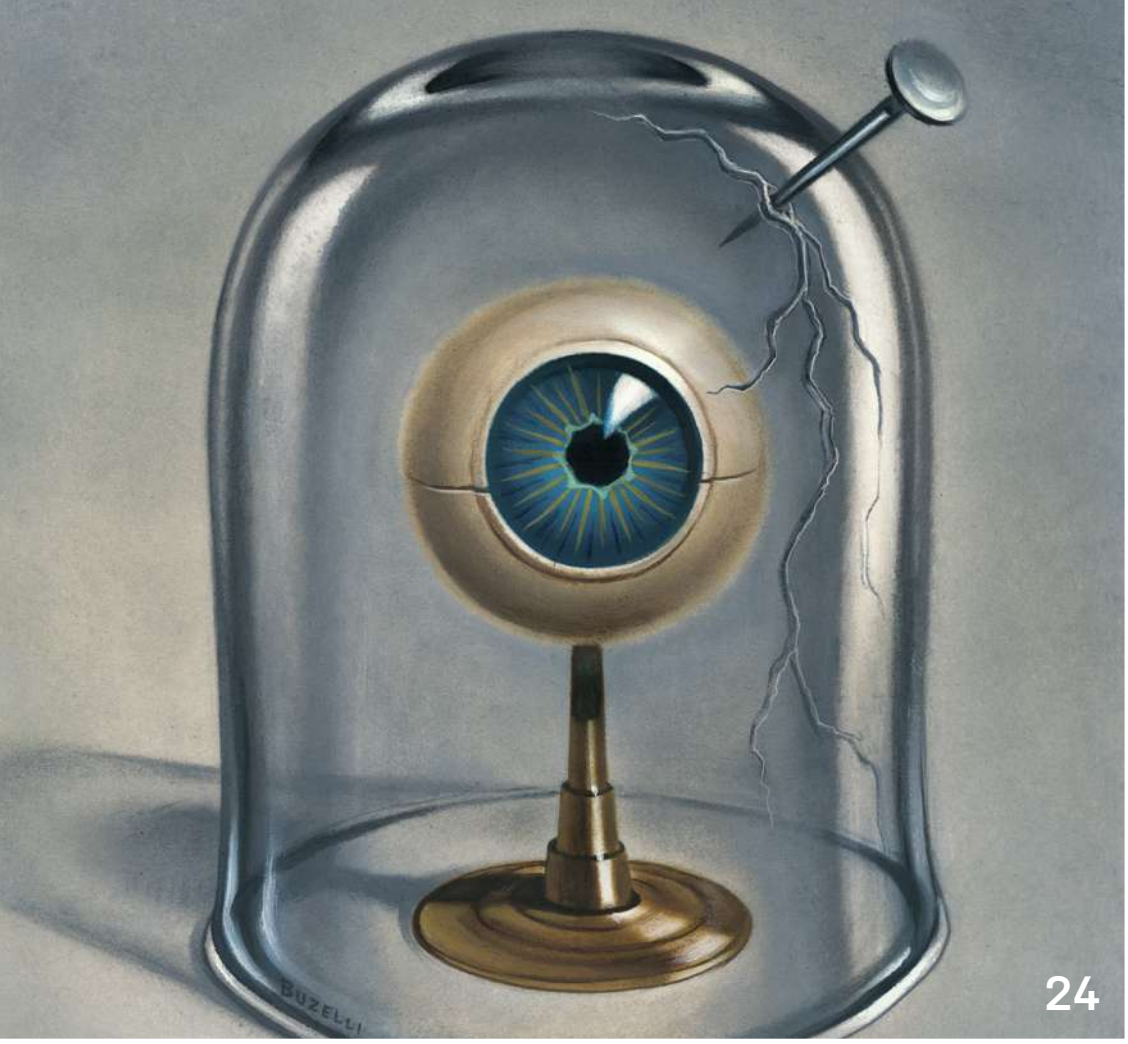
SPRING 22

proto

MASSACHUSETTS GENERAL HOSPITAL //
DISPATCHES FROM THE FRONTIERS OF MEDICINE

Teachable Moments

For almost a century, Case Records has explored thorny medical mysteries for the world's clinicians. p24



contents

SPRING 2022

STAT

POST-OP

FEATURES

on the cover

Each of the Case Records of the Massachusetts General Hospital is chosen for its educational value—and some remain enshrined in the collective memory of medical professionals.
// Illustration by Christopher Buzelli

proto: a prefix of progress, connoting first, novel, experimental. Alone, it conjures an entire world of the new: discoveries, directions, ideas. In taking **proto** as its name, this magazine stakes its ground on medicine's leading edge—exploring breakthroughs, dissecting controversies, opening a forum for informed debate.

proto

EDITORIAL ADVISORY BOARD
Stephen B. Calderwood, M.D.
Alasdair K.T. Conn, M.D.
Jeffrey B. Cooper, Ph.D.
Mason W. Freeman, M.D.
Daniel A. Haber, M.D., Ph.D.
Daniel B. Hoch, M.D., Ph.D.
Lisa Iezzoni, M.D.
Robert E. Kingston, Ph.D.
David Louis, M.D.
Joan W. Miller, M.D.
Harry W. Orf, Ph.D.
John A. Parrish, M.D.
Celeste Robb-Nicholson, M.D.
Jerrold F. Rosenbaum, M.D.
Nathaniel M. Sims, M.D.
James H. Thrall, M.D.
Joseph P. Vacanti, M.D.

MASSACHUSETTS GENERAL HOSPITAL

David F.M. Brown, M.D. // President, Massachusetts General Hospital
Marcela del Carmen, M.D., M.P.H. // President, Massachusetts General Physicians Organization
Peggy Slasman // Editor-in-Chief
Sarah Alger // Senior Editor
Michael Morrison // Social Media Editor

Dotdash meredith

Diane di Costanzo // Vice President, Editorial
Jason Anthony // Editor
David Bumke // Project Editor
Emily Silber // Managing Editor
Isha Sharma // Associate Editor
Syndi Becker // Executive Design Director
Matt Hageman // Art Director
Geoff Chadsey // Photo Editor
George J. Baer III // Vice President, Client Partnerships
Cynthia Manalo // Senior Director, Client Partnerships

Founded in 1811, Massachusetts General Hospital is a 1,043-bed academic medical center located in Boston. It is a founding member of Mass General Brigham (formerly Partners HealthCare) and is the original and largest teaching affiliate of Harvard Medical School.

DIAGNOSIS IS INHERENTLY FASCINATING. There's a certain thrill associated with sifting through clues in a patient history, studying data and images, drawing on deduction, logic, judgment, experience and knowledge to find an answer. Diagnosis represents the vital key that opens the arc of care, and in the high-stakes practice of medicine, it is an art and science that must be learned, practiced, honed and respected.

The forum known as the clinicopathological conference—CPC—is designed to do just that. This storied teaching tool brings together experts to present, listen, probe and ponder medical mysteries. Some of the most interesting and illustrative cases discussed during CPCs here are published as "Case Records of the Massachusetts General Hospital"—a staple within *The New England Journal of Medicine* since 1924.

In the past two years, case researchers at the MGH and in other COVID-19 hotspots looked to the CPC as a tool to examine intriguing cases and inform the medical profession about this viral threat. Recent CPCs have explored complex questions about COVID and its manifestations—a 68-year-old man with acute kidney injury, a 74-year-old man with acute respiratory failure, a 47-year-old woman with a lung mass, a 66-year-old homeless man.

This latest use of CPCs and Case Records—a tradition highlighted in this issue of *Proto*—builds upon more than a century of history. In 1915, MGH internist Richard C. Cabot, who pioneered the case method of medical education at Harvard Medical School, published the first Case Records for some 800 subscribers. Since then, more than 7,000 published case studies have taught generations of physicians how to work their way through conundrums of diagnosis and treatment.

Late in 2020, after the first wave of the pandemic, Eric S. Rosenberg, editor of Case Records and director of the MGH microbiology laboratory, and David N. Louis, MGH Pathologist-in-Chief, collected 10 of the COVID Case Records for a hard-covered volume. "We believe that this shared experience cumulatively represents the very best of Massachusetts General Hospital in our mission to care for our patients and care for each other, while striving to learn from our experience and teach others," they wrote in the preface. "Our hope is that, as we strive to end this catastrophic pandemic, these cases will someday soon be of only historical value."

We hope so too.

DAVID F.M. BROWN, M.D.
President
Massachusetts General Hospital

MARCELA DEL CARMEN, M.D., M.P.H.
President
Massachusetts General Physicians Organization

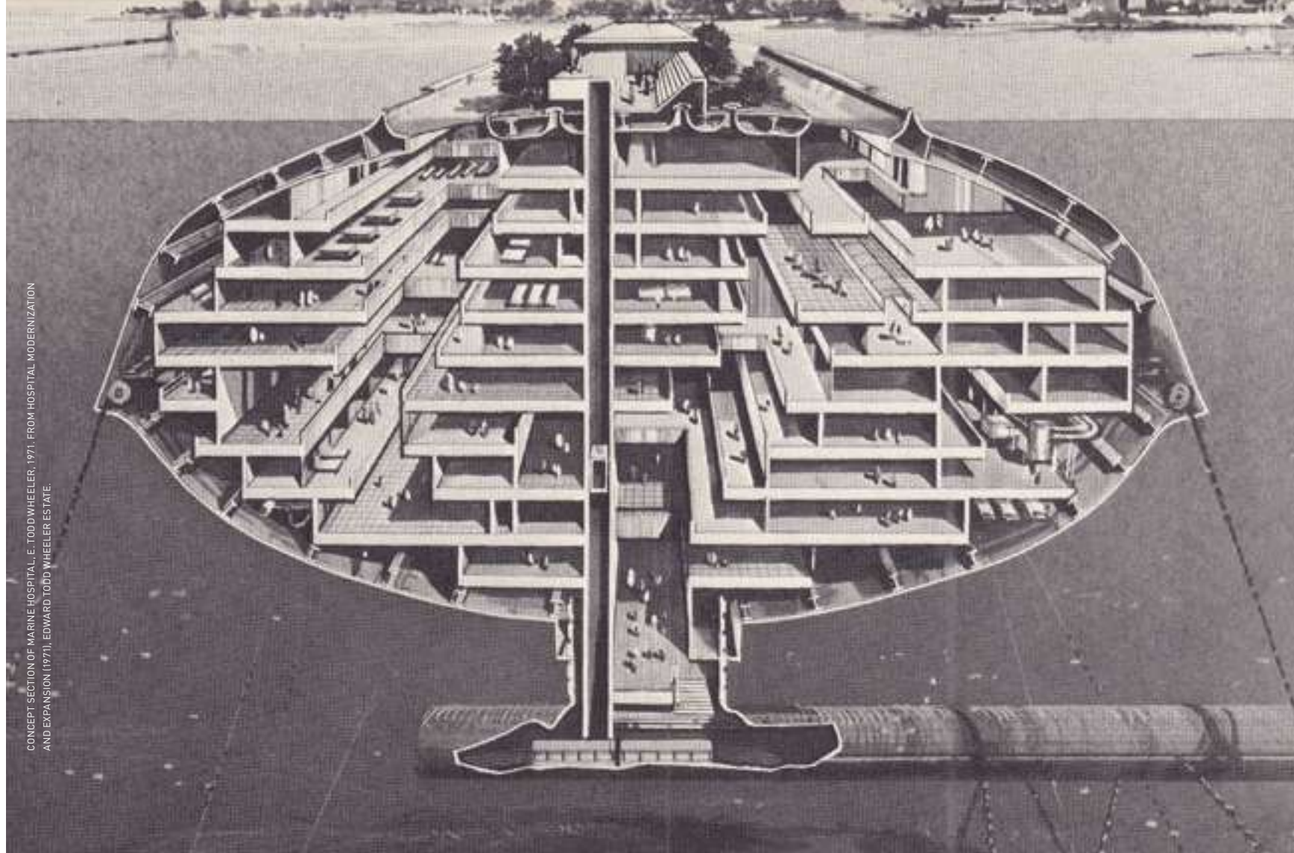
Facebook.com/protomag @ProtoMagazine ProtoEditor@MGH.Harvard.edu

stat

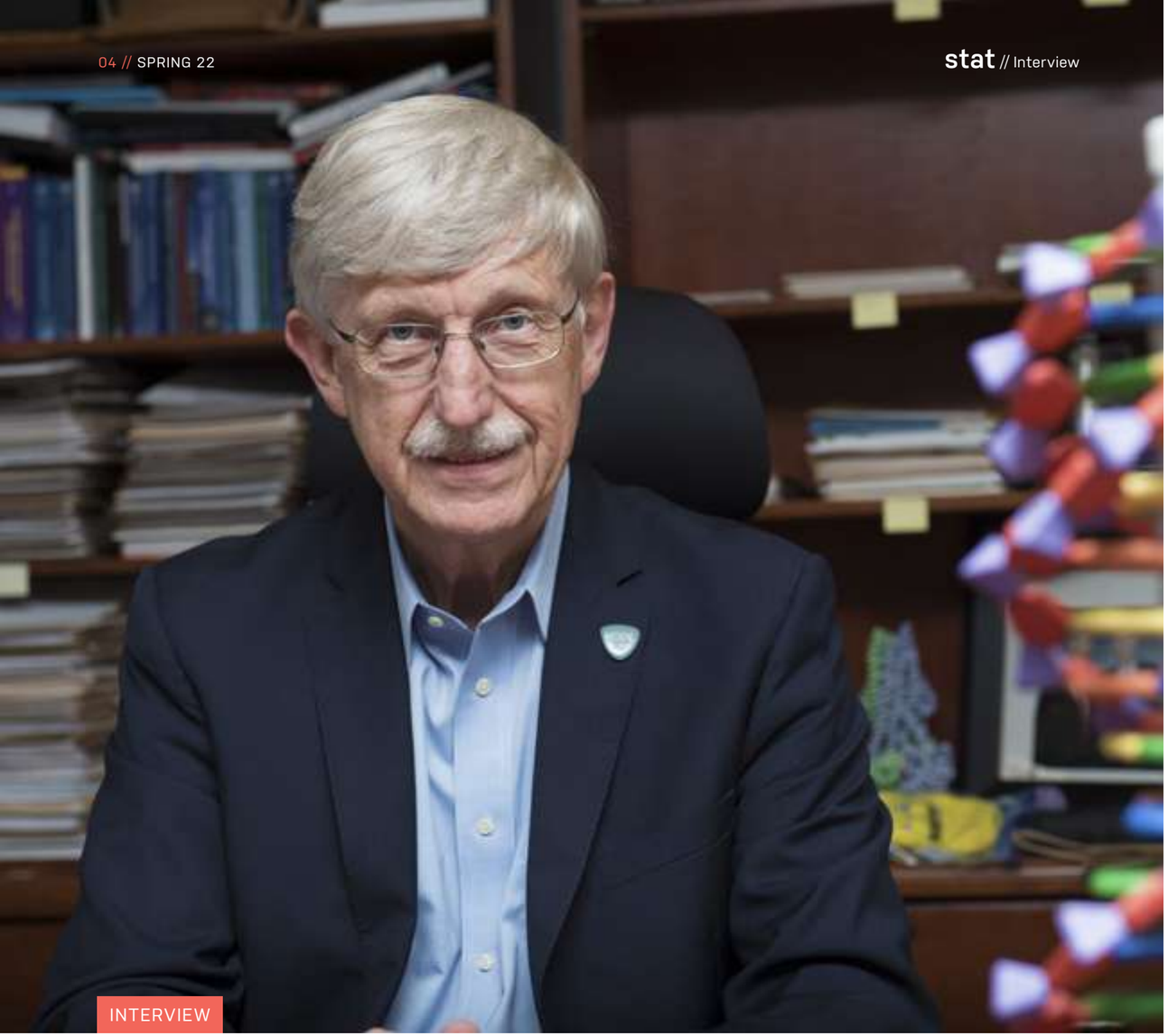
FOCUS

Architect E. Todd Wheeler created a number of whimsical floor plans for hospitals in the 1960s and 1970s. Among them—this "Marine Hospital," which is entirely underwater. The idea grew from the notion that sterile environments help patients the most. "Hospitals were the first buildings to seal themselves off from the outside world, where contamination is uncontrolled," says Michael P. Murphy Jr., an architect and co-author of a recent book on hospital design, *The Architecture of Health*.

Ideas have since changed. Murphy and his colleagues, for instance, designed the Butaro District Hospital in Rwanda, a 2008 project that used natural ventilation to combat the chronic, nosocomial transmission of tuberculosis. The book, which looks at architectural innovation throughout the centuries, also serves as a companion to "Design and Healing: Creative Responses to Epidemics," an exhibition running until February 2023 at the Cooper Hewitt, Smithsonian Design Museum in New York City.



CONCEPT SECTION OF MARINE HOSPITAL, E. TODD WHEELER, 1971. FROM HOSPITAL MODERNIZATION AND EXPANSION (1971). EDWARD TODD WHEELER ESTATE.



INTERVIEW

The Secret Life of Francis Collins

Even in his new national advisor role, the former NIH director maintains a pipeline of personal research projects.

In December 2021, Francis Collins stepped down as head of the National Institutes of Health—a position he had held for a record 12 years—only to be tapped a few months later to serve as acting Science Advisor to the President of the United States. Yet even in the national spotlight, Collins has always preserved a private lifeline to his first love—the trenches of genetic research.

In the 1970s, with a doctorate in chemistry and an M.D., Collins found himself drawn to the field—even when peers said genetics would never be practical, "except perhaps in pediatrics." His career has consisted of proving those critics wrong. Collins's early laboratory at the University of Michigan pioneered work in cystic fibrosis, and in 1993 he was asked to head the Human Genome Project, an unprecedented global collaboration that completed a map of the sequence of human DNA in 2003. As NIH director, Collins oversaw and nurtured the revolution in genetics that project helped spark.

OPPOSITE PAGE: SAIT SERKAN GURBUZ/ASSOCIATED PRESS.
THIS PAGE: THE NOUN PROJECT

Q: Had you ever planned on a life in public service?
A: Not really. When I got the call to join the NIH, there was some resistance on my part because I was enjoying myself. I was running a research lab, taking care of patients and teaching. Part of my negotiation for the job was a request to continue my own research at a modest scale. And I've run that research lab at NIH for 28 years.

Q: One focus of your lab has been progeria, a rare disease that causes accelerated aging. How did that come about?
A: When I was a fellow in training at Yale in 1982, I was assigned the care of a patient with progeria. Nothing was known about the cause. Much later I met a White House fellow whose son had just been diagnosed. I had a postdoc in 2001 who was looking for a new project. The genetic cause of progeria would be really hard to discover, since it didn't recur in families, so many of the tricks we had access to at the time didn't apply. But we said, "OK, let's give it a year." In less than a year, we had it. It's a single base pair misspelled in the middle of exon 11 of the lamin A gene.

Q: Did that lead to any therapeutics?
A: Yes. Soon after discovering the mutation and studying the biology of lamin A, we thought, "Maybe this could benefit by treatment with a drug developed for cancer," a farnesyl transferase inhibitor. Lonafarnib is now an FDA-approved treatment, capable of extending life by a few years. But that's not good enough—we're currently exploring two other, much more targeted approaches. One tries to block the abnormal RNA from getting translated. That's looking really promising, and in our mouse model, it extends life span by a factor of almost two.

Even more dramatically, we are exploring *in vivo* gene editing in a collaboration with David Liu at the Broad Institute of MIT and Harvard. To our amazement, a single intravenous infusion of a gene editor carried by the AAV9 vector almost cured the disease in our mouse model. So we are now very fired up to work toward a human trial.

Q: You're also looking at type 2 diabetes—a much more common condition.
A: Yes. The disease has very clear hereditary contributions, which you can tell just by examining family pedigrees. But when we started to study it, it was resistant to any simple models that Mendel would have appreciated. It had to be polygenic.

Well, now we know just how polygenic it is. There are at least 243 regions in the human genome that carry variants that increase the risk of type 2 diabetes. Currently we understand how those variants work for maybe a third of those. But five years ago, we understood almost none. So we're making real progress, and each clue leads us to potential therapeutic targets.

Q: Any advice to researchers about leaving their labs to engage in public life?
A: I would say—don't be afraid to get out in public. It's challenging, but it's much needed. At our current moment, there's a distrust of science at a level that I have not seen before. So we all have a responsibility to go out and counter that. Scientists have a great story to tell. If you can learn to talk about the work you do in terms that anyone can understand, you're going to see people's eyes light up.

BY THE NUMBERS

Minimal Cells

580,076

Number of genetic base pairs in *Mycoplasma genitalium*. It has the smallest genome of any naturally occuring bacterium that can be grown in the lab, making it the subject of studies to understand most basic workings of the genome.

531,560

Number of base pairs in JCVI-Syn3.0, the first synthetic "minimal cell." Created in 2016, Syn3.0 boasts the smallest genome of any known organism—with only 473 genes to *E. coli*'s 4,000 and *M. genitalium*'s 482.

60

Number of additional genes that scientists say could theoretically be removed from Syn3.0 without rendering it nonviable—although its growth rate would likely slow to a crawl.

149

Number of genes in Syn3.0 with functions that remain unknown. If they are removed, however, the cell becomes nonviable. The number represents about a third of the genes in the minimal cell, a number that demonstrates how far the understanding of the most basic, life-sustaining work of the genome has yet to go.

10

Hours that it took a computer to simulate 20 minutes of the minimal cell cycle, using the NVIDIA Titan V graphics processing unit. A 2022 study created a complete computer model of Syn3.0 so that researchers could closely study chemical reactions and precise components of this most basic form of life in 3D.

INFOGRAPHIC

An Atlas of Atlases

International collaborations are mapping the human body, atom by atom.

BY JOSHUA A. KRISCH

In 2003, the Human Genome Project created widespread excitement when it completed a map of human DNA. That moonshot also, indirectly, kicked off an era of unprecedented global collaborations. Dozens of other efforts soon got underway, each one trying to comprehensively map a dimension of the human body and make that information freely available to scientists around the world.

Some of those projects have wrapped up; many more are ongoing. Here are some of the more notable efforts to create medical reference works that will endure for decades to come.

KEY:

DATE DENOTES START OF STUDY

ONGOING STUDY

COMPLETE STUDY

COMPLETE/ ONGOING STUDY

Nearly 150,000 types of human cells have been identified.

CELL ATLASES

Human BioMolecular Atlas Program (2017) A project of the National Institutes of Health looks at the the function of all cells of the body and their relationships.

Atlas of Fetal Gene Expression (2020)

Endoderm Reference Atlas (2021)

Platelet Expression Atlas (2021) A Chinese effort to list how platelets in blood respond to infection and injury.

Allen Cell Types Database (2015)

Human Cell Atlas (2017) This aims to categorize all 37 trillion cells in a healthy body.

Gut Cell Atlas (2019)

Cambridge Cell Atlas (2018)

Single Cell Expression Atlas (2018)

Transcriptomic atlas of the human retina

Lung Cell Atlas (2019)

Atlas of the peripheral immune response to severe COVID-19

BRAIN ATLASES

Allen Human Brain Atlas (2010) The first comprehensive brain map links gene expression data to discrete 1-millimeter portions of the brain.

RNA ATLASES

Extracellular RNA Atlas (2016)

R2 RNA Atlas (2019)

miRNA Tissue Atlas (2016)

Small RNA Expression Atlas (2017)

ExoRBase Atlas of mRNA, lncRNA, circRNA (2017)

This 2020 resource categorized cell responses to COVID-19.

Metabolic Atlas (2020)

Tissue Atlas (2015)

Subcellular Atlas (2017)

PROTEIN ATLASES

Human Protein Atlas (2018) This inventory of proteins is one of the most visited biological databases in the world.

Brain Protein Atlas (2020)

Pathology/ Cancer Atlas (2017)

Blood Atlas (2019)

It occupies more than 15 million web pages.

Human Proteoform Atlas (2020) More than 57,000 proteoforms—variant forms of proteins—are cataloged here.

Immuno-Proteoform Atlas (2021)

Neuro Proteoform Atlas (2021)

Cardiac Proteoform Atlas (2020)

Cancer Proteoform Atlas (2020)

PATH-OLOGY ATLASES

Microbe Atlases

Atlas of SARS-CoV-2 Translatome and Transcriptome (2021)

Clostridium difficile Antimicrobial Resistance Atlas (2021) A roundup of more than 10,000 genomes of C. diff, a bacterium that presents a danger in health care settings.

virusMED Atlas of Viral Proteins (2021)

Cancer Genome Atlas (2010) The U.S. effort provides detailed molecular information on 33 types of cancer.

ImmReg Regulon Atlas (2020)

Pan-Cancer Atlas (2018)

Single-cell Tumor Atlas (2021)

It generated 2.5 petabytes of publicly available data.

MSJONESNYC

DEFINED

\ek-spō-sōm\

Exposome

n: The measure of an individual's total environmental exposures.

Genetic mutations have been found to account for only about 10% of human disease. The rest result from the roulette wheel of environmental factors, including chemicals, microbes, food and light.

Yet researchers know little about how most exposures predispose the body to disease. The term exposome was coined in 2005 as a move to kick-start research. The word describes every nongenetic driver of health and includes not only external factors but chemicals naturally produced within the body by inflammation, oxidative stress and gut bacteria.

Mapping the astronomically complex exposome and its impact has proved difficult, though recent strides have been made. One 2021 study looked at the blood of pregnant women and newborns and detected more than 100 chemicals, 55 of which had never been reported before. A large effort in Utah is looking to trace the lifetime exposome of people with age-related diseases to look for correlations with air quality and other factors.

A new device, StrandDx, was also recently granted FDA breakthrough status in December 2021. It analyzes the chemicals in a strand of hair, a coded "printout" of the exposome that developers say can assess the likelihood that a baby will develop autism. Previous research has shown that some with autism metabolize atypical levels of some metals, which would appear in hair. The company plans similar tests to help in the diagnosis of inflammatory bowel disease and cancer.

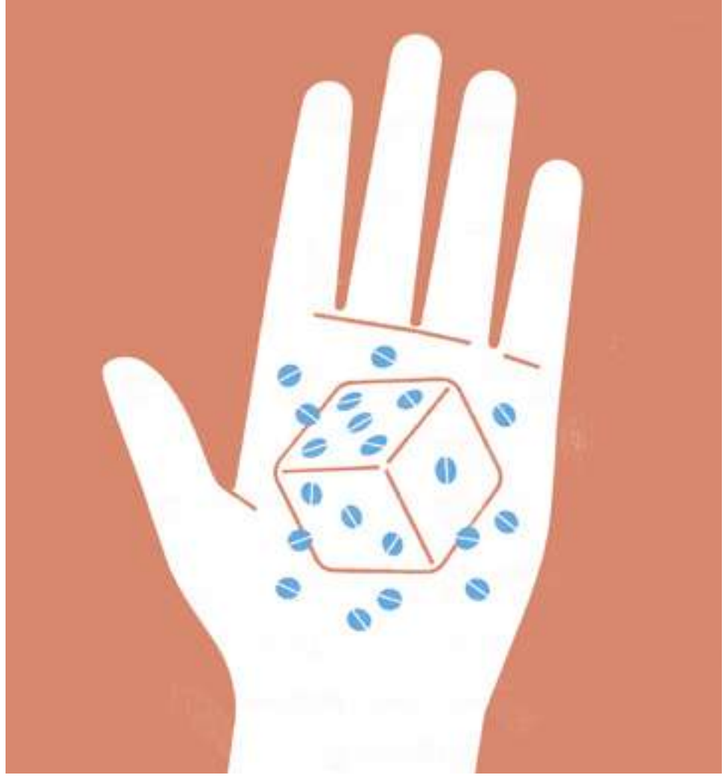
Yet others hope to bring the study of the exposome as close as the makeup counter. The beauty company L'Oréal announced in January 2022 that it would partner with Verily, a sister company of Google that focuses on health research, to "discover the links between exposome, skin aging and deep biology of the skin."

POLICY

I'll Take My Chances

Patients with terminal cancer now have more treatment options. Will that help or hurt?

BY STEPHEN ORNES



Cancer clinical trials are how new treatments get to patients. But in recent years, cries for reform of that system have gotten louder. One significant obstacle is recruitment, as only about 1 in 20 people diagnosed with cancer joins clinical trials, and nearly 40% of clinical trials close without meeting enrollment targets.

In June 2021, the U.S. Food and Drug Administration released a draft of new recommendations designed to expand patient eligibility for clinical trials. Their primary target: people with incurable disease. Historically, most trials have required a cancer patient to try approved treatments before moving on to experimental therapy, even if existing treatments only briefly prolong life. But under the new guidelines, a patient with no avenues to a cure may immediately join a trial for an unproven drug.

Some welcome the new guidance. "In some cases new drugs are the best options for the patient," says Katherine Arline, chief strategy advisor at Shepherd Foundation, a 501(c)3 committed to driving change for rare cancer patients. Her foundation filed a comment in support of the new guidance, as patients with rare cancers may be particularly likely to benefit, she says.

Others applaud how the new guidance gives patients and their providers greater control of treatment decisions. The FDA guidance recommends that patients be informed about the potential benefits of the new drug, as well as benefits of other available treatments. "Let a smart and consenting patient, together with a conscientious physician, go through that informed consent process and be the main arbiter of who gets on a trial," says Raymond Osarogiagbon, an oncologist at Baptist Cancer Center in Memphis, Tennessee, who led a recent evaluation of eligibility criteria that was published in *Clinical Cancer Research*.

> Some see increased patient agency as a double-edged sword.

Others, however, see increased patient agency as a double-edged sword. Patients and physicians may be drawn to a clinical trial because the drug is new and unknown, without appreciating the slender chances of success, warns clinical research fellow Mark Lythgoe at Imperial College London. In a review of new cancer drugs receiving FDA accelerated approval, only 20% demonstrated a meaningful benefit in prolonging overall survival in confirmatory trials, he notes.

"Many patients may not be adept at interpreting evidence and making an accurate risk-benefit analysis," says Lythgoe. For many diagnoses, he says, patients would be equally or more likely to benefit from existing treatments that have already gone through rigorous clinical trials.

With hematologist-oncologist Vinay Prasad at the University of California, San Francisco, Lythgoe recently published two commentaries—in *Nature Reviews Clinical Oncology* and in the *Journal of Cancer Policy*—that outline the risks of the new guidance. They worry, for example, that a patient diagnosed with metastatic HER2+ breast cancer might pass up drugs shown to extend life by years in favor of a new drug that has not demonstrated any benefit in humans before.

Lythgoe says he hopes the "appropriate informed consent" process described in the FDA guidance would prevent such scenarios. The FDA, he says, has already made it easier to enroll in cancer trials, most recently through recommendations finalized in July 2020. In that document, patients with brain metastases, who are often excluded because of their poor prognoses, could join more clinical trials.

"That was a step in the right direction," Lythgoe says. But he believes this newer draft guidance opens the door to potentially worse outcomes. "For me, it needs to have a more established framework, to describe when taking a chance on a new, unproven drug might not be appropriate," he says.

The comment period for the new guidance closed Aug. 24, 2021, and the FDA has not said when finalized guidance will be published. For many, the change would be a win both for treatment investigations and patients who want to see all of their options. "As a default, everybody should have access to promising trials," says Osarogiagbon. "For safety or efficacy we can look at excluding this or that type of patient. But then at least it's a rational clinical choice and not a rule coming down from on high."

ILLUSTRATION BY CHRIS GASH

UPDATE

The Beset Brain

A theory about the cause of Alzheimer's moves forward.

BY SARAH DIGIULIO

Since the 1990s, some researchers have been gathering evidence for a radical reimagining of what causes dementia. The antimicrobial protection hypothesis, first proposed by biochemist Bob Moir and Rudolph Tanzi, director of the Genetics and Aging Research Unit at Massachusetts General Hospital, suggests that amyloid proteins that build up in the brain aren't a waste product, accumulating as we age, but rather are part of an immune response to protect the brain against infection. ("Why Plaque Attacks," Winter 2017.)

Recent work has added support to that idea. One focus has been on the herpes simplex virus, which may infect young people then lead their immune systems to form plaques and tangles to protect against it. Over decades, those plaques and tangles could trigger the brain inflammation associated with Alzheimer's disease.

Large recent studies have indeed shown that people diagnosed with a severe herpes simplex infection earlier in life were at higher risk of developing Alzheimer's disease. A 2018 study of more than 30,000 Taiwanese adults showed that herpes simplex infection increased risk of dementia 2.56-fold. Yet taking antiviral medication cut the risk of developing dementia by 90%.

A 2021 study involving patients in Wales, Germany, Scotland and Denmark, however, found a much lower association between treatment with antivirals and a decreased risk of dementia.

One reason for the different results could be the role of a genetic mutation—the APOE4 allele—that has been linked to a significant increase in the risk of Alzheimer's disease, says Ruth Frances Itzhaki, a visiting professor at the University of Oxford. Her work has shown an association between the APOE4 allele, herpes simplex virus type 1 infection in the brain and Alzheimer's disease. "If the investigators had included only people carrying APOE4, the protective effect would very probably have appeared greater," Itzhaki says.

Now a small U.S. trial will test whether the antiviral valacyclovir can help people with Alzheimer's disease who are also infected with herpes simplex virus type 1 or 2. But Tanzi has doubts about whether the drug will help those already showing signs of Alzheimer's. While a viral infection from long ago might be driving brain pathology, the plaques, tangles and inflammation linked to Alzheimer's disease develop decades before symptoms. Still, antivirals might help if givern early enough, Tanzi says, preferably pre-symptomatically in those with recurring viral infections.

Tanzi's current research is attempting to determine when the damage of Alzheimer's first occurs and when it becomes irreversible. His team is analyzing the plaques in autopsied brains of those who have died with Alzheimer's to search for traces of DNA evidence that an infection might have started the pathological process decades before symptoms.

ILLUSTRATION BY JONATHAN ROSEN

MILESTONE

A Rose for Dora Richter

In 1922 the Berlin woman became the first to undergo gender-affirming surgery.

BY HANNAH THOMASY

The words *per scientiam ad justitiam*—through science to justice—are chiseled on the simple gray tomb of Magnus Hirschfeld. The physician is best known for founding Berlin's Institute for Sexual Research in 1919, breaking the ice on the modern study of sexuality. This year marks another achievement—the centenary of the first gender-affirming surgery, which Hirschfeld and his Institute made possible.

Transgender lives during Hirschfeld's time were often made criminal, and arrests were common for wearing clothes of a gender different from the one physicians assigned at birth. One of Hirschfeld's early victories was persuading the German police to issue "transvestite passes," based on medical opinion, which gave permission for some to dress as they wished. The Institute also provided support for trans people and helped them find employment. For the sexual minorities of the time, says Brandy Schillace, historian and editor of the *BMJ*'s *Medical Humanities* journal, Hirschfeld's Institute was something like the opposite of conversion therapy: "It let you be yourself among other people who also recognized you as yourself."

Dora Richter, who worked as a maid at the Institute, became the first recorded case of complete gender affirmation surgery. She was born male in the Erzgebirge region of Germany in 1891 to a relatively poor farming family. Her desire to live as a girl was apparent from an early age: She had a strong dislike for boys' clothes and attempted to remove her penis by using a cord as a tourniquet at the age of 6. During her childhood, her family let her live as a girl.

How Richter made her way to the Institute is a matter of speculation. Some propose that she wanted someone to help her after an arrest for cross-dressing, which was punishable by up to six weeks in prison. Rainer Herrn, a senior lecturer at the Institute for History of Medicine and Ethics in Medicine at the Charité University Hospital Berlin, says that her visit was more likely prompted by seeing a popular film featuring the work of Eugen Steinach.

Steinach was a pioneer in the study of sex hormones who, in one experiment, had transplanted a male guinea pig's testes into a female. "The film proposed the revolutionary idea that animals can be transformed from one sex to another," says Herrn. Hirschfeld's Institute also played a role in the film, so Richter may have gone there to ask whether it was possible to have the procedure herself.

Richter's years at the Institute seem to have passed pleasantly—she was finally able to live as a woman, around other people who accepted her, and a few transwomen also lived and worked there. Ludwig Levy-Lenz, a physician associated with the Institute at the time, described their easy camaraderie: "I shall never forget the sight one day when I happened to go into the Institute's kitchen after work: there they sat close together, the five 'girls,' peacefully knitting and sewing and singing old folk-songs." During this time, Richter also received a series of surgeries that would, just as she had hoped, transform her. She received an orchiectomy in 1922, followed by a penectomy and vaginoplasty performed several months apart in 1931.

This period of relative calm did not last, however. The circumstances of her death remain a mystery, but many speculate that she was killed when Nazi supporters ransacked the Institute in May 1933 or shortly thereafter. Hirschfeld himself died in exile in France in 1935.

While legal protections for trans people have improved in many areas of the world, they still face discrimination, harassment and violence. Similarly, while surgical frontiers are advancing every year, with tissue engineering techniques creating more functional genitalia and facial and vocal procedures providing better alignment with gender identity, access to that medical care remains fraught.

One main obstacle is coverage by health insurance plans. The public health exchanges set up under President Barack Obama barred participating insurance plans from discriminating based on gender identity, a step taken to protect gender-affirming care. But the next administration removed that protective language, and a recent proposal to reinstate it for the 2023 exchanges has met with pushback from insurers and conservative groups.

In 2015, more than half of coverage requests for gender-affirming surgery were denied. Insurance coverage for facial surgery is an especially difficult obstacle as many insurance companies do not deem it to be medically necessary, despite evidence of its importance.

In all, Hirschfeld might be proud of the movement he—and Dora Richter—helped to usher in. While many of his ideas on sexuality became dated, some of his remarks suggesting gender and sexuality as a spectrum seem prescient. In 1910 he wrote that "the number of actual and imaginable sexual varieties is almost unending; in each person there is a different mixture of manly and womanly substances, and as we cannot find two leaves alike on a tree, then it is highly unlikely that we will find two humans whose manly and womanly characteristics exactly match in kind and number." That full spectrum in gender-affirming care is only now beginning to find its place in medicine.

SECOND OPINION

Bias a Blind Spot

The *JAMA* podcast at the heart of "Confronting bias in journals" (Fall 2021) should remind us of the importance of managing our blindspots. Beginning drivers are taught about space that is unobservable in mirrors and requires craning one's neck to check for other vehicles. Ignoring this blindspot can prove disastrous.

Similarly, failing to detect our biases when we look in the mirror is less about their absence than it is of our failure to recognize and check our blindspots. Awareness of biases is often a precursor to curbing their impact. Just as a patient who denies being obese is unlikely to increase activity or alter their diet, reviewers, editors, or physicians who deem themselves unbiased often contribute to the continuance of racial (and other forms of) injustice. Society seems to have conflated being unbiased with being a good person, stemming widespread denial that bias exists or we harbor any.

Let's be clear: Being biased doesn't make you a bad person, it makes you human. Our morality comes into question when we elect to ignore, accept, or double down on our biases. Simply, you cannot fix a problem by pretending it doesn't exist.

Derek R. Avery, Ph.D. // C. T. Bauer Chair of Inclusive Leadership, Bauer College of Business, University of Houston

A Call to Humility

The article "Confronting Bias in Journals" addresses the critically important topic of how we address equity in medical research and knowledge generation. The cited examples, while current, echo a history of troubling and discriminatory practices. I am reminded, for example, of the Baltimore Lead Abatement Study conducted in the 1990s, which was unfavorably compared to the Tuskegee Study and yet managed to be published in medical literature.

Structural racism is real and deeply rooted in American institutions, including health care. Health care leaders are not immune to prejudice, bias, even racism. Patients endure safety, quality, and financial consequences when we fail to act equitably. I take these as statements of fact—but if there is any disagreement, it is precisely the role of journals and their leadership to settle these questions through thoughtful policies that publish and promote relevant research. The article points out a number of actions some journals are taking, and which should be widely adopted. Arriving at the right policies can begin with relatively easy actions: embrace humility and empower representative diversity in every board, committee, panel, and organization. Structural changes and real inclusivity will drive necessary reforms.

Shantanu Agrawal, MD, MPhil // Chief Health Officer, Anthem, Inc.

WHAT'S YOUR TAKE? Send your comments or suggestions for future topics to protoeditor@mgh.harvard.edu.

THE TRUST CRISIS

Respect for the advice of medical authorities has hit a new low. What happened, and how can it rebound?

As someone who manages 13 chronic and recurring conditions, including diabetes and kidney disease, Claire Sachs relies on a fleet of providers to help her make choices about treatment. "Literally to survive, I have to put my trust in a lot of people," says Sachs, who works as a patient advocate in Maryland. Since childhood, she has been in and out of physicians' offices and hospitals, and occasionally a misdiagnosis or unsuccessful therapy has tested her faith in the health care system. Through the years she has fine-tuned where to place her trust, in part based on practitioners' credentials and expertise, but also on a feeling of security and transparency when she's in their office. She understands that this quality is hard to put into words, and even harder to generalize beyond her own experience. "What one person needs and expects from a physician to build trust may be very different from what someone else is looking for," she says.

Yet however trust is defined, it is essential to the practice of medicine. Trust is the foundation of the physician-patient relationship, and a high level of trust has been shown to lead to improved experiences for patients and better compliance and outcomes. In the larger context of health care, a measure of trust is required in relationships throughout the system—between clinicians and their employers, between health officials and the public, between insurers and hospitals. That variable web of trust is crucial, if difficult, to measure and track, says Lauren Taylor, assistant professor at NYU Langone Health. "Trust is powerful," Taylor says. "When it's there, you can move ahead, often with better results—because everyone is on board. But when trust is absent, everything grinds to a halt."

Increasingly, that trust is waning. The proportion of people who express "quite a lot" to "a great deal" of confidence in the medical system slid from 73% in 1966 to 44% in 2021. People of color, those younger than 50 and those with less education and lower incomes all have lower-than-average levels of trust in health care. And in terms of being trusted by its citizens, the U.S. health care system fares worse than many others, ranking 19th in a 2021 global ranking, far below developing countries such as India, Thailand and Nigeria.

As it drags on, the COVID-19 pandemic continues to shake trust in health care, and it comes at a time of declining confidence in government, business, organized religion, higher education and the news media. "The collapse in trust has an

By Linda Keslar // Illustrations by Jacques Kleynhans

epidemic quality to it," says Robert Blendon, emeritus professor at the Harvard T.H. Chan School of Public Health, who has researched the topic for decades.

A lack of trust during the pandemic has almost certainly worsened consequences. As of January 2022, the United States ranked 59th in the global vaccination race, lagging behind many nations with higher trust in their health care systems, and distrust has also fueled rebellion against masking and other measures to limit the spread of COVID-19. That harm will outlast the pandemic, both for public health and individual patients, says physician Richard J. Baron, president and CEO of the American Board of Internal Medicine (ABIM)—which certifies one in four doctors in the United States—and the ABIM Foundation, a nonprofit established in 1989 to advance medical professionalism and improve health care. "Looking ahead, distrust will continue to undermine how patients receive and relate to medical recommendations of all kinds," he says.

This creates an urgency not only to define trust but to implement solutions that could help rebuild and sustain it, says Baron. "There's an opportunity for health institutions to make trust-building a core priority, a cornerstone of better health," he says.

• • • •

Today's worries about trust would have seemed novel during most of the early history of medicine. Patients weren't asked to trust their physicians; rather, they were instructed to do so. The Original Code of Medical Ethics, issued by the American Medical Association in 1847, required patients' "obedience" to their physicians' recommendations. But in 1925, in a lecture to students at Harvard Medical School later published as an essay, "The Care of the Patient," Francis Weld Peabody called for a relationship built on reciprocal trust. "The care of a patient must be completely personal," said the Boston physician, and this could occur only if patients opened up to their physicians about all of the concerns and ailments they had, a deeper personal knowledge that would lead to the best care options.

Peabody's essay remains on many medical schools' curricula, and for decades after it was published, medicine was dominated by the kind of personal, trusting relationships between doctors and patients that he described. Solo practitioners made house calls, and "if you asked average Americans in 1950 whether they trusted the health care system, their answer would likely have been, 'what system?' " Taylor says.

But public confidence in medicine peaked in the mid-1960s. The decline afterward may be surprising, considering how much medical progress was made. Yet other kinds of "progress" have been less welcome, says Blendon. Hospitals grew and consolidated into health systems and insurance companies further inserted themselves into the physician-patient relationship. Increasingly forced to interact with people they didn't know, many patients came to feel anonymous and vulnerable, Taylor says.

At the same time, medical practitioners have found themselves working in increasingly impersonal systems that require them to move patients in and out of the office briskly, leaving them little time to establish meaningful rapport. Indeed, lack of time with their doctors is a chief complaint of patients who say they don't trust them. Those patients' attitude is, "I won't trust your knowledge until I know you care," says Daniel Wolfson, executive vice president of the ABIM Foundation.

Two reports by the Institute of Medicine—"To Err is Human," released in 1999, which explored medical errors and patient safety, and "Crossing the Quality Chasm," in 2001, which called for higher-quality care—also contributed to public mistrust of the profession. While the reports had a positive impact on the practice of medicine, highlighting needed changes and pointing out mistakes, they shattered illusions about the infallibility of health care. Some patients, reading about the reports in their newspapers, began to feel that there were cracks in the system.

The pandemic has introduced an entirely new phase of uncertainty. In a recent survey, about a third of people said their trust in the health care system decreased during the pandemic, compared with only about one in 10 whose trust grew stronger. One population with continued distrust is those who have traditionally lacked equal access to health care. Those in underrepresented groups often have a history of discrimination from providers and many have suffered a disproportionate number of COVID-19 deaths. One recent survey found that Black respondents were twice as likely as whites to say they have experienced discrimination in a health care facility—and those who had been discriminated against were twice as likely as others to say they don't trust the system.

Others who have lost trust fall on the far ends of the political spectrum. As journalistic and institutional trust among these groups has faltered, "truth decay" sets in, in which the value of medical facts is increasingly discounted. With the proliferation of misinformation online and in social media, many Americans now have trouble distinguishing fake news from factual accounts, and an unceasing torrent of medical misinformation has contributed to suspicion of physicians and their guidance.

Attacks from politicians have further undermined trust in public health officials. One particularly vexing charge is that these officials sometimes change their recommendations about COVID-19 preventive measures, which detractors say sows doubts about their truthfulness and the value of their advice. Almost half of Americans in a recent survey said they don't trust the Centers for Disease Control and Prevention, and even fewer trusted their state health departments. That poor relationship has added suspicion around their guidelines for vaccines, mask wearing and business restrictions.

> A third of people said their trust in the health care system decreased during the pandemic.

Members of the public aren't the only ones losing trust in the system. Almost a third of physicians, stretched thin by dealing with wave after wave of the pandemic and beset by shortages in protective gear and other challenges, said in a recent survey that their trust in the health care system and their organizations' leadership had decreased; 43% said they trusted government health agencies less than they did before COVID-19. "Particularly at the beginning of the pandemic, the news changed every day about what we should do in terms of protecting ourselves and our patients and treating this disease," says Jarrett Weinberger, who practices at Detroit Medical Center and is an associate professor at Wayne State School of Medicine.

At the same time, however, some physicians have said they now trust each other more than they did before the pandemic. "There's a sense, by now, that we're all in this together and we need to support each other," Weinberger says.

• • • •

Against this backdrop of declining trust and its consequences, there's an urgency for researchers to learn what can be done to rebuild it, says NYU's Taylor, who recently coauthored a study that analyzed more than 750 papers on trust published during the past 50 years. She says that finding consensus about how to measure trust is challenging, as is the road to practices that might help increase it.

Stimulating more research is one objective of the Building Trust initiative, a national campaign that the ABIM Foundation launched in 2018. Several dozen collaborators, including hospitals and health care systems, specialty societies, health plans and consumer organizations, have signed on to explore how to elevate trust while also looking at the related goals of reducing systemic racism in health care and addressing medical misinformation.

As part of that effort, the foundation issued a Trust Practice Challenge, which invited organizations to submit approaches they've used to help build or rebuild trust. One entry featured long-standing efforts at

Massachusetts General Hospital to build trust through shared decision-making. Providing decision aids to patients improves their knowledge, reduces conflicts about care decisions and helps patients clarify what they want from their treatment, says Karen Sepucha, director of the Health Decision Sciences Center at MGH and an associate professor at Harvard Medical School.

Shared decision-making can be particularly critical in building trust with patients considering surgery, Sepucha says, and in a recent study, she and her colleagues tested decision aids that provided information about the benefits and risks of surgical interventions for osteoarthritis of the hip and knee, herniated discs and spinal stenosis. Armed with accurate information about their choices, patients were better able to share their views with their surgeons. "It's not about persuading patients to adopt one treatment over another," Sepucha says. "Decision aids help patients guide us as much as we're guiding them." After the decision aids were implemented, patients reported better communication with their doctors and a higher level of trust.

Another winning submission to the Trust Practice Challenge is a case study about UnityPoint Health Prairie Parkway LGBTQ Clinic in Iowa. Kyle Christiason, a family practice physician, helped found the clinic nearly five years ago after his eldest child, then a preteen, came out as a transgender boy. Finding culturally competent care for their child required a four-hour drive from their rural town. "The origin of our clinic started with a recognition that it was absurd to have to travel that far just to get the care our child needed," says Christiason.

The LGBTQ community has long experienced discrimination and other health barriers, putting people at heightened risk for mental health problems such as depression, addiction and risk for suicide. In addition, patients are less likely to access preventive care, such as cancer screenings. "The trust crisis here is particularly pronounced, with about one in five physicians declining to provide care to transgender patients," Christiason says, though often less because of bias than a lack of training. "My suspicion is many physicians don't feel equipped," he says.

Christiason approached his employer, and in 2018, UnityPoint designated two nights a month to provide primary care and some specialty care for LGBTQ patients. Some changes, such as asking for patients' chosen names and for their pronouns, were designed to build trust by letting patients know this was a place that understood their concerns. Clinicians also became fluent in addressing treatment issues affecting this patient population. The organization also provided additional training for staff.

> Shared decisions can be critical in building trust.

Today, the clinic provides care to 300 patients, double its initial roster, and UnityPoint has opened a second LGBTQ clinic in Des Moines. "This approach is not only a replicable model for LGBTQ care, but also a framework for clinical care for any marginalized and vulnerable population," Christiason says. "What sets it apart is the depth of thought and consideration given to every interaction, decision and connection." It has built trust in patients whose previous experiences with the medical system often left them feeling wary and excluded.

In Dallas, other methods were used to foster trust in a community that had long been underserved. "To build trust you have to move beyond the walls of the hospital," says Fred Cerise, a physician who serves as president of Parkland Health and Hospital System in Dallas, one of the largest public hospital systems in the country. "We asked people in our community to reflect on what we can do better," he says, a process that has led to numerous substantive changes.

One initiative that came out of that effort is RIGHT Care, through which Parkland behavioral social workers work with rapid-response teams from the fire department and police to help patients experiencing behavioral health emergencies. The program, in its fourth year, now diverts about a third of such encounters away from busy emergency rooms and jails. A paramedic, police officer and social worker are all part of a team that responds to 911 calls identified as a mental health crisis. Teams are assisted by a mental health clinician in the 911 call center. Together the team focuses on how to handle behavioral health situations, stabilize patients on the scene and connect them with community agencies that provide social health services and medical attention.

• • • •

These experiments show several approaches that could help rebuild trust in medicine, and others are sure to emerge. Yet they come at a time when cheers for the "health care heroes" of the pandemic have, in many cases, given way to virulent attacks on medicine and its practitioners. Medical misinformation has become an online industry, and at least half of U.S. states have adopted laws making it harder for state and local agencies to protect public health. Trust, it seems, may become another casualty of the pandemic, and the implications are far reaching, says Adriane Casalotti, chief of public and government affairs for the National Association of County and City Health Officials, which represents nearly 3,000 local health departments across the country. Local health officials are a first line in offering the public factual, life-saving information, "and if they are not allowed to do their job and give correct science information because of an anti-science political agenda, the outcome will be that people get sick and may die," Casalotti says.

"There is no single magic bullet that can cure the problem of misinformation and everything that comes with it," says Adam Berinsky, Mitsui professor of political science at the Massachusetts Institute of Technology. But there are incremental solutions that can make a difference, he says. Even if patients don't know what to believe, and don't trust the health care system, most still trust their own physicians. "So that's the person who needs to be delivering the information," Berinsky says. "If we can rebuild trust physician by physician, and reach some people some of the time, it can lead to better outcomes."

Restoring trust in public institutions, their leaders and in science and medicine overall is going to be a long, difficult process, says Blendon. Yet as the country emerges from the pandemic, it might adopt an approach used after 9/11 to get at the truth of what happened and reassure the public that steps are being taken so that it can't happen again. Blendon and others envision establishing bipartisan commissions at the federal, state and local levels to examine how public agencies lost credibility with the public. "We need to step back and make sure that in the future, these issues are not polarized by partisan politics ever again," he says.

DOSSIER

BuildingTrust.org, ABIM Foundation. The online clearinghouse for the Building Trust project has case studies, videos, opportunities to network and updates on progress.

"A Trust Initiative in Health Care: Why and Why Now?" by Timothy Lynch et al., *Academic Medicine*, April 2019. The authors describe the importance of trust in health care, examine reasons for the decline, including larger societal trends and others specific to health care and the need for champions.

"The Future of Health Policy in a Partisan United States," by Robert Blendon et al., *Journal of the American Medical Association*, April 2021. The paper explores profound political divisions on key issues of health care policy—COVID-19, universal coverage and national health insurance reform, U.S. health care system reform, and race and disparities in health care—and their implications for the future.

TOGETHER IN *sickness* AND *health*

Humans share three out of five infectious diseases with animals. New solutions are gently bridging the species divide.

The precise origin of COVID-19 is still uncertain. But whether it came from a bat or not, the virus now passes freely between humans and animals—pigs, rabbits, tigers, bats, white-tailed deer, mink, house cats, bank voles, ferrets and gorillas, to name a few. The pandemic crosses borders not only between nations, but barriers between species, so efforts to contain its spread will have to account not only for human politics but also managing ecosystems and populations of wild animals—where the disease can reside, evolve and emerge again as a lethal threat.

In that sense, COVID-19 joins the majority of known infectious diseases, about 60% of which can spread to and from nonhuman animals. These so-called zoonotic diseases, a long-standing burden, are a problem that keeps growing.

"Over the past 50 or 60 years, newly recorded zoonotic viruses have been spilling over to humans at a pretty constant rate of about two per year," says Andy Dobson, a professor of ecology and evolutionary biology at Princeton University who studies wildlife diseases. "But the proportion that create epidemics and pandemics is increasing." About three out of four new infectious diseases now come from animals.

"Emerging zoonotic infectious diseases are here to stay," says Casey Barton Behravesh, director of the One Health Office at the Centers for Disease Control and Prevention. One Health began more than a decade ago as an international effort to look at a wide range of health-related interactions between humans, animals and environments. "Preventing future outbreaks

BY *Adam Bluestein*

ILLUSTRATIONS BY *Amandine Urruty*

requires an approach that includes collaboration across the human health, animal health and environmental spectrum," Behravesh says.

This idea of stewardship of global ecology stands in stark contrast to the current pandemic response, which has focused on what to do *after* a virus spreads widely. Dobson and other experts argue that rather than spend vast sums trying to contain a global contagion, the nations of the world should make investments in "safeguarding nature" to prevent zoonotic pandemics from occurring in the first place. In a February 2022 article in *Science Advances*, Dobson and other members of a global task force argued that targeting some causes of disease spread, such as deforestation and the wildlife trade, could cost as little as $22 billion a year—or about 2% of the economic and mortality costs of the COVID-19 pandemic, which economists predict could reach $10 trillion to $20 trillion.

But it's not only new diseases that pass to people from the animal kingdom. Researchers also continue to be concerned about endemic vector-borne diseases such as malaria and dengue, which refuse to be eradicated. Climate change and other factors, such as busy global travel routes, have enlarged the natural ranges of those diseases' host species and made them more of a threat than ever. Dengue cases alone have increased more than eightfold over the past two decades, says Dobson, and "more kids still die every day from malaria than people who were killed in 9/11."

International consensus moves slowly, however, and expensive global initiatives are likely to be a hard sell. A more feasible approach may be to target the natural world tactically. Such interventions must avoid the tragic mistakes of DDT, which destroyed entire ecosystems in the effort to kill the mosquitoes that carried malaria. Today, researchers are pursuing gentler approaches to block diseases in the animals before they can transmit them to humans.

"It's going to take different forms of control," says Dobson, "because the things we currently have to kill with—insecticides and poisons—aren't specific enough. We need more creative ways of working with nature, more creative solutions and less of a despotic, 'kill everything' mindset." The past few years have delivered several landmark advances that may fit that bill. Taken together, innovations in vector management could slow the advance of zoonotic disease, a desperately needed step.

• • • •

The *Aedes aegypti* mosquito is the primary vector for Zika, chikungunya and dengue, a flavivirus that causes flu-like symptoms in about 96 million people a year. Because *Ae. aegypti* mosquitoes live in urban and semi-urban environments throughout the tropics and subtropics, they've been especially hard to control with insecticides. Those chemicals can affect other species too, including humans, and when they do reach their targets, mosquitoes are often quick to build up immunity. "Driving up and down the street with trucks of fogging insecticides is largely a waste of time," says Scott Ritchie, a medical entomologist and principal investigator in the Bill & Melinda Gates Foundation–funded Eliminate Dengue program.

Ritchie and his colleagues at the nonprofit World Mosquito Program, led by medical entomologist Scott O'Neill, have experimented with an alternative approach. They found that a promising bacterium of the *Wolbachia* genus can be introduced into mosquito colonies as its own epidemic. Infection with this pathogen blocks the insects' ability to transmit dengue. In one of the first large-scale field tests of the technology, Ritchie and other researchers introduced a total of 4 million *Wolbachia*-infected *Ae. aegypti* mosquitoes to insect populations in and around Cairns and Townsville, Australia. Soon, almost all of the local target mosquitoes had the bacteria, and there has been almost no local transmission of dengue since the program's launch in 2013. The approach was then tried in Yogyakarta, Indonesia, which saw a 77% drop in reported cases.

Ritchie and his team infect mosquitoes with a strain of *Wolbachia* called *wMel*. Although it doesn't naturally infect *Ae. aegypti*, the *wMel* strain is able to take up residence in those mosquitoes in an arrangement called endosymbiosis. Inside the insects' cells, *wMel* competes for nutrients that the dengue virus needs for replication. "They still get infected and hold virus in their gut, but the amount in their salivary glands is significantly reduced, so that can't transmit it," says Ritchie.

A much bigger prize would be malaria, which is transmitted to humans through the bite of female *Anopheles* mosquitoes and kills more than 600,000 people annually, according to the World Health Organization. So far, however, progress has been limited. In 2013, researchers at Michigan State University led by Zhiyong Xi established the first stable line of *Wolbachia*-infected *Anopheles stephensi*—a common malaria vector in urban India. Although those infected mosquitoes were too weak to spread effectively through wild populations, Xi and other teams have since managed to introduce the bacterium into two additional *Anopheles* species that cause malaria in Africa.

A controversial innovation called a gene drive might eventually help turn malaria's tide. Instead of introducing an infection, as in the *Wolbachia* approach, the gene drive uses CRISPR gene-editing technology to inhibit a mosquito's ability to reproduce or to carry the parasite that causes malaria. Programmable guide RNA is inserted into the genome of a mosquito, and as the gene-drive mosquitoes breed with others, that genetic variant spreads through the population by capitalizing on the "selfish" quality of some genes.

In nature, some genes improve on the 50-50 odds that they'll be inherited by offspring. The CRISPR edit mimics this process using a construct on one chromosome. During an early stage of development, the CRISPR part of the gene drive finds and

A BETTER NEIGHBOR TO NATURE

The One Health initiative advocates a comprehensive global approach.

Respecting Habitats

Encroaching on wild spaces makes outbreaks more likely.

Antibiotics

Dialing back the use of these in livestock leads to fewer drug-resistant bacteria in humans.

Tighter Surveillance

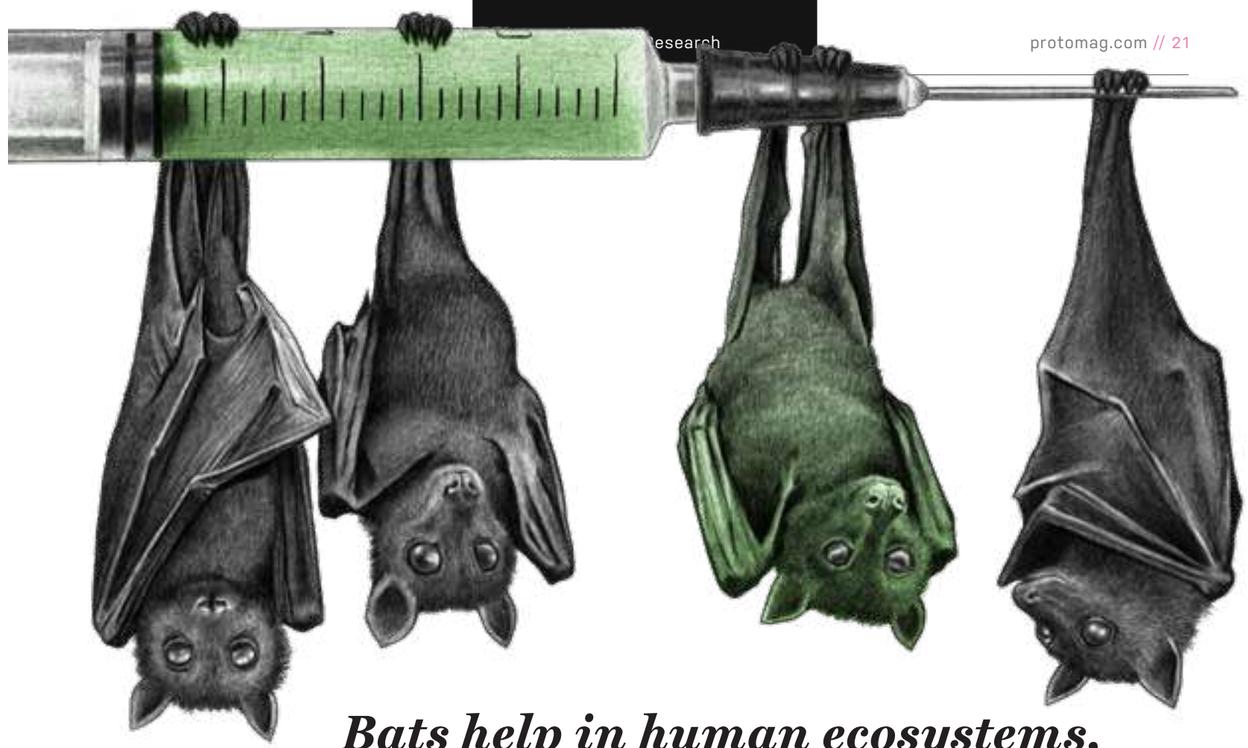
Monitoring livestock and wildlife can spot pathogens earlier.

More Vets

Animal health specialists are especially critical in Africa, but their numbers are currently low.

Disease Management

New tools that target disease, not carriers, are the goal.



Bats help in human ecosystems, so efforts should target the diseases, not the animals.

cuts out the normal gene on the opposite chromosome. The gene drive then serves as a template when that cut is repaired, resulting in a mosquito that now carries two copies of the modified gene, bringing the inheritance rate to nearly 100%.

While gene drives might be used to reduce or wipe out wild populations of mosquitoes, in some cases that might simply clear out an ecological niche for a worse vector. Instead, scientists from the University of California, Irvine, UC Davis and Federal University Oye-Ekiti in Nigeria recently tested a gene drive that blocked transmission of the malaria parasite in *Anopheles gambiae*. Within six generations, or about six months, every mosquito had at least one copy of the gene-drive construct. That's well within one annual malaria transmission cycle and suggests that gene drives might ultimately be part of an effective control strategy.

• • • •

Long before bats were investigated as the first vector for COVID-19, they were known for transmitting other diseases, including rabies. Yet bats also do good work—for example, by devouring insects at a rate that would otherwise require at least $3.7 billion in annual pest control costs in the United States, according to the National Park Service. Bats are also important as pollinators and seed spreaders, which means that targeting disease in bats should do its utmost to protect the bats themselves.

In Mexico and Latin America, vampire bats (*Desmodus rotundus*) are the principal spreaders of rabies, and topical anticoagulant poisons, which spread from bat to bat, are frequently used. But these poisons might affect the wider environment, and mathematical modeling suggests that it would require intensive, coordinated culls across impractically large areas to reduce rabies rates.

Since the early 2000s, researchers have studied whether it was possible to vaccinate the animals instead. Topical oral vaccines could spread to members of a colony in much the way that poisons are currently transmitted. "Vampire bats are highly social and they do a lot of grooming of each other," says Daniel Streicker, a Wellcome Trust senior research fellow in the Institute of Biodiversity, Animal Health and Comparative Medicine at the University of Glasgow in Scotland. His lab is currently exploring two types of "self-spreading" vaccines for inoculating bats: transferable vaccines, which spread only from treated bats; and transmissible vaccines, which can spread infectiously through multiple generations.

In a 2019 paper in *Nature Ecology & Evolution*, Streicker and his fellow researchers from the University of Michigan used field experiments and mathematical modeling to show that a transferrable topical vaccine could spread at high enough rates to inoculate a large fraction of a bat colony. At locations in Lima, Peru, they captured roughly a quarter to a third of bats in colonies of 200 to 250 animals. They applied a gel containing a biomarker that shows up as bright-orange fluorescence in the animal's fur once it's ingested, and then released the affected bats. At the end of four weeks, an estimated 84% of bats in one colony showed the fluorescent marker, and 92% of bats in another had it.

Streicker believes his group's work on transmissible rabies vaccines, still at an earlier stage than the development of transferable vaccines for bats, could ultimately help limit the spread of other diseases such as Nipah virus and Hendra virus that infect humans on a periodic, recurring basis. Such a vaccine could provide lasting immunity for bat populations, and new vaccines could be developed as potentially dangerous diseases appear.

• • • •

Deer ticks are the agents through which the bacterium *Borrelia burgdorferi* infects humans with Lyme disease, a potentially debilitating illness that is still incompletely understood. In the United States, Lyme disease is the most common infection transmitted from animals to humans, and reported cases have nearly doubled since 2004.

Erol Fikrig's laboratory at Yale University School of Medicine wants to address the problem by implementing a new kind of vaccine. Vaccines generally work by priming a body to repel the virus or bacteria that invades the body and causes harm. Fikrig's project targets the vector—the tick itself—rather than the pathogen it carries, an approach that could be game-changing for zoonotic disease.

When a vector animal bites someone, it can sometimes add a cocktail of salivary compounds—anticoagulants or anti-inflammatory agents—that bypass the skin and a local immune response. In deer tick saliva, for instance, Fikrig's group identified 19 key proteins. His mRNA vaccine—the same kind of vaccine that has proved so successful in protecting against COVID-19—trains the body to fight those proteins that help the *B. burgdorferi* bacterium take hold. (*B. burgdorferi* itself has proven resistant to vaccine development.)

The result is that the body reacts more vigorously to the tick's bite, making it harder for infection to occur. In a guinea pig study published in *Science Translational Medicine* in November 2021, bites of vaccinated animals became red and inflamed within 18 hours, alerting them to the tick. Because Lyme bacteria can take a day or two to be transmitted, this early warning could be a game changer in humans by alerting them to a tick bite that might normally go undetected.

The study also found that ticks didn't hang on to vaccinated guinea pigs for as long.

This vaccine uniquely targets the carrier, not the disease.

"Normally, ticks feed for four to five days on a guinea pig," says Fikrig. "These ticks seem to come off at about two days, and their weights were lower. It's like they took a little meal and maybe were nauseous, and just gave up. It's a slow-transmitting pathogen, so if we can really change the feeding behavior, we have the capacity to prevent transmission," Fikrig says.

Fikrig says the same kind of vaccine could also help with other slow-transmitting tick-borne diseases, including babesiosis, a rare but occasionally life-threatening disease found in the United States. The current vaccine would be unlikely to work against others, such as the emerging Powassan virus, which is transmitted from tick to host in about 15 minutes. There is also more basic science to do, says Fikrig, who notes that the current vaccine worked in guinea pigs but not in mice, and thus might not yet be effective in humans.

Indeed, while new barriers against animal-borne disease are sorely needed, caution has been the watchword, especially when efforts have ventured into new territory. Forests are not hospitals, and researchers are keen to avoid unintended consequences that they cannot be on hand to oversee. Gene drives in particular, because they send a cascading genetic change through wild populations, have raised biosafety concerns, and environmental groups and governments have issued strong warnings about their use. Proponents of the technology now are seeking to develop new strategies and safeguards.

Some vaccines for bats have been tested in captive environments, and researchers say they might be ready for use in the wild in another five years or so. Other bat vaccines that spread infectiously between populations could be 10 years away. Nonetheless, the University of Glasgow's Streicker sees his lab's work as part of a fundamental shift in approach—away from trying to manage emerging diseases only after they've begun to infect livestock or humans. "Now we think we can intervene earlier in that process," Streicker says, "and instead of just killing these animals, we may be able to make them less effective transmitters of diseases that we don't want to have jumping into people."

DOSSIER

CDC.gov/onehealth/zohu, Zoonoses and One Health Updates. One-hour monthly webinars from the Centers for Disease Control and Prevention cover emerging health threats at "the animal-human-environment interface."

"Epidemiology and biology of a herpesvirus in rabies endemic vampire bat populations," by Megan E. Griffiths et al., *Nature Communications*, November 2020. The researchers look at a transmissible rabies vaccine for vampire bats, using a betaherpesvirus as a vaccine vector.

"Gene Drives Gaining Speed," by Ethan Bier, *Nature Reviews Genetics*, August 2021. This review paper describes how gene-drive systems work, different types of gene drives and potential strategies for their deployment.

FOR NEARLY A CENTURY, THESE PATIENT HISTORIES HAVE ILLUMINATED AND ADVANCED THE ART OF MEDICINE.

CASE RECORDS

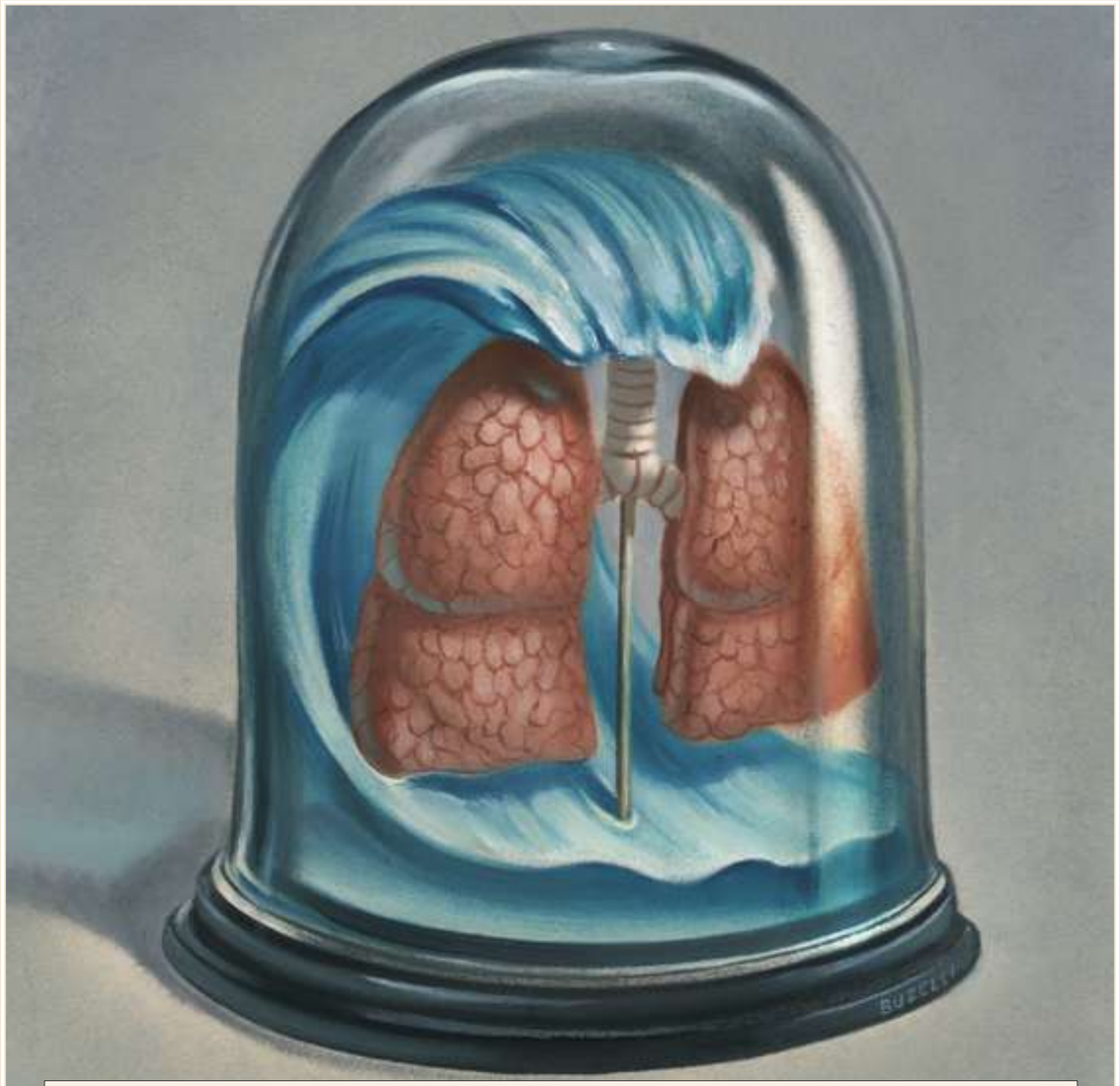
of the Massachusetts General Hospital

BY ANITA SLOMSKI // ILLUSTRATIONS BY CHRISTOPHER BUZELLI

Massachusetts General Hospital's clinicopathological conferences, or CPCs, are the shop talk heard around the world. On this afternoon in 2017, an audience of physicians has packed into the White Surgical Amphitheater for Surgical Grand Rounds. Allan Goldstein, surgeon-in-chief at MassGeneral Hospital for Children, lays out the case of conjoined twins, just 22 months old, and how a team of over 50 surgeons and 150 other health care providers prepared, planned and performed their separation—knowing that saving one girl meant the other would die.

A CT scan on the screen shows the twins joined from the chest down to the pelvis, an anatomy that uniquely shares a single liver, bladder, intestinal tract, urogenital and circulatory system. Separating them would be a tricky task, fraught with ethical challenges, and 20 other hospitals had refused to do the procedure. Now Oscar Benavidez, chief of Pediatric Cardiology at MGHfC, talks about meeting these tiny patients, describing how they played and sang, the one protecting the other, swatting away a needle when her sister got a blood test. The main concern was that Twin A, in addition to being noticeably smaller and weaker, had a tenuous cardiac status. She was missing a main pumping chamber of her heart and had irregular blood vessels running between her heart and lungs. An enlarged mesenteric artery, which normally supplies the intestine with blood, served as Twin A's lifeline, transmitting blood and oxygen from her sister—but it wasn't enough. Twin A had developed recurrent pneumonia and her oxygen levels were dangerously low. She was dying, and because she shared a circulatory system with her sister, her death would leave little or no time to intervene to save Twin B, Benavidez says.

Brian Cummings, chair of the Massachusetts General Hospital Pediatric Ethics Committee, steps up to describe



The Case of the Lingering Tsunami

A young woman encounters a natural disaster and a rare condition.

The 17-year-old had trouble breathing, severe right-side muscle weakness and couldn't speak intelligibly when she was transferred to the U.S. hospital ship *Mercy*. Seven weeks earlier, she had been swept up by a tsunami, and MGH physicians on the *Mercy* found she had a collapsed lung and lesions in her brain probably caused by a bacterial infection. The diagnosis: tsunami-related aspiration pneumonia, or "tsunami lung," caused by microbes in water and mud she had taken in. Treated with antibiotics, she improved steadily, and on the day she was discharged, she "burst into peals of laughter," according to the Case Record.

how he and his colleagues wrestled with the moral considerations of the case. Were the conjoined twins one person or two people? Is it ever morally acceptable to sacrifice one person over another? In an earlier court case, a judge had ruled that if one twin could survive, it was mandatory to operate, whatever the parents might want. But who ought to have the decision to perform separation surgery? The MGH committee ultimately left the decision to the girls' parents, who made the agonizing choice to move ahead.

A flurry of slides—preoperative imaging and tactical models—show the surgeons' plan to separate them. The physicians walk their audience through the 14-hour procedure. Although Twin A did die during surgery, Twin B not only survived but, there in the front row, sits with her parents in the audience, a tiny figure among the physicians. Just over a year older now, the girl smiles and claps along with the rest of the audience. According to her team, she now has a normal life expectancy.

That CPC would go on to provide the bones of Case 33-2017—one of "the Case Records of the Massachusetts General Hospital," a staple of *The New England Journal of Medicine* since the 1920s. The medical story of these conjoined twins would join nearly 7,000 other cases that have, over the decades, developed a global following. "In 2020, Case Records was viewed more than a million times by readers from more than 200 countries," says University of Pennsylvania pulmonologist Darren Taichman, deputy editor of *NEJM*.

From their earliest days, Case Records have been selected for their suitability as teaching tools, showing physicians how to diagnose and treat medical disorders and conundrums. Many cases have seared themselves into the collective memories of readers. There was the case of a 54-year-old man who went into cardiac arrest after eating too much licorice; the patient whose surgeon did the wrong procedure—carpal-tunnel surgery instead of trigger-finger release—and also operated on the patient's healthy hand; the woman whose mysterious symptoms traced back to a traditional Ayurvedic medication, which turned out to be giving her lead poisoning.

EVERY CASE RECORD HAS TO PROVIDE AN EDUCATIONAL OPPORTUNITY.

"Every case has to provide a fundamentally significant educational opportunity," says Eric Rosenberg, the sixth and current editor of Case Records, who directs the microbiology laboratories at MGH and is a professor of pathology at Harvard Medical School. While there may be fewer medical mysteries than in the 1920s—and diagnostic tools are significantly more advanced—even the most knowledgeable physicians encounter new puzzles, says Scott Podolsky, an MGH internist who is professor of global health and social medicine at Harvard Medical School and director of the Center for the History of Medicine at the Countway Medical Library at HMS. "There will always be emerging diseases, such as COVID-19, say, or conditions that arise from the effects of climate change," he says. The Case Records discussions have also evolved to focus on emerging treatments and protocols, including diagnoses as they get further refined—what was called "lung cancer" in the past, for instance, is an ever-evolving collection of subtypes.

The greatest accolade for the Case Records may be how widely it has been emulated. Academic medical centers around the world now use the clinicopathological conference model, Rosenberg says, and many medical journals present mystery cases for readers to solve. The format has also caught on in consumer publications, such as the *New York Times* and *Washington Post*. Perhaps this popularity derives from Case Records being a fundamental kind of human puzzle—what has gone wrong with this person and how can the patient be made well? That puzzle strikes to the heart of medicine and helps set the craft apart from other disciplines.

When Walter B. Cannon was a Harvard Medical School student in 1898, he was subjected to a very different style of medical training—four-hour daily lectures that he found to be "dreary and benumbing." Cannon envied his roommate, a student at Harvard Law School, who learned in a much more hands-on way, through real legal cases provided by his teachers. Cannon believed that the same type of educational format could work for medicine, too. At his urging, MGH internist and HMS professor Richard C. Cabot adopted what came to be known as the case method, in which students no longer regurgitated facts but discussed "actual cases of disease."

Soon Cabot decided it wasn't just students who could benefit from this approach, and in 1910, he teamed up with James H. Wright, the hospital's first full-time pathologist, to present cases of deceased patients. They decided to put an expert on the spot, almost in the style of a modern game show, presenting the facts to house officers and visiting physicians and challenging them to come up with the correct diagnosis. Each Thursday at noon, a CPC was convened at the Allen Street Amphitheater—if an autopsy was in progress, the body was quickly shunted to the morgue and the autopsy table covered with a white sheet. A physician took the stage and worked through the patient's history while those in the audience questioned him about his methods. He would finish by offering a diagnosis, which was then compared with the results of the patient's autopsy.

These teaching exercises proved so popular that Cabot began publishing the cases. In 1915, four records a week were mailed to roughly 800 subscribers, who paid $5 a year. Then, in 1923, the inaugural "Case Records of the Massachusetts General Hospital," edited by Cabot and his son Hugh, appeared in *The Boston Medical and Surgical Journal* (which later became *NEJM*).

Although Cabot had made his reputation as an expert diagnostician, it was important to him to show that even his medical knowledge had limits. Once, when a medical student asked during a CPC whether Cabot had considered rheumatic pneumonia as a diagnosis, he replied, "That's a good idea; I never thought of it." In fact, the student's diagnosis was confirmed by autopsy. That idea of confronting fallibility also became an important contribution of the Case Records. "Too often in current medical literature we get accounts of brilliant successes, rather than of failures in diagnosis and treatment, which are of far higher educational value," noted an editorial in the *Boston Medical and Surgical Journal* a few months after Case Records launched.

• • • •

The Case Records soon grew into a medical institution. Cabot edited them until 1935, choosing the cases and then discussing them himself, often without preparation. The next three editors followed the same model. It wasn't until 2002, when the reins were taken by Nancy Lee Harris, a hematopathologist at MGH, that the formula saw changes. Cases had historically focused on mystery diagnoses and their solutions, but while Harris was discussing the project one night with her husband, a radiation oncologist at Dana-Farber Brigham, "he pointed out that because laboratory medicine and imaging had become so good at uncovering a diagnosis, that was no longer the biggest

The Case of the Remedy Gone Wrong

An older woman's health gets worse as her daughter tries to help.

The 76-year-old had abdominal pain and constipation, had lost weight, was disoriented and had considered suicide. A history of domestic abuse led to a diagnosis of post-traumatic stress disorder, and anti-anxiety medication helped.

But the search for an explanation of her abdominal pain hit one dead end after another. Finally, because her urinary porphyrin levels were high, and other test results pointed toward possible acute intermittent porphyria, she received four days of treatment with hemin. Yet the symptoms she had expereinced, they saw, could also signify lead poisoning.

It turned out that the patient's daughter, who lived in India, had been providing dietary supplements thought to include traditional Ayurvedic medicines—which often contain lead, arsenic and mercury. Further testing revealed blood lead levels more than 20 times higher than normal. She received chelation therapy, and six weeks later, although her blood lead levels remained high, her abdominal pain was gone, she was eating better and her thinking had improved.

In Depth • Meducation

The Case of the Eye Transfixed

A lawn maintenance accident leads to a perilous surgical journey.

The 27-year-old was in agony. While maintaining his yard, the weed whacker he was using had kicked up a long nail that shot into his right eye, and just trying to open it caused excruciating pain.

As his doctors approached treating the injury, they worried that the embedded nail might be the only thing preventing a cascade of brain damage, and pulling it out could cause a life-threatening hemorrhage. Advanced CT imaging couldn't reveal whether the nail had punctured the internal carotid artery.

One option, bringing its own catastrophic risks, was to drill into the skull and also make an incision in the neck, providing access for emergency repairs. Finally, though, with two surgeons standing ready to make those cuts, a third gently pulled out the nail—and nothing happened. Even the eye was saved. With a course of antibiotics to prevent infection, the patient was released from the hospital, and within eight weeks, his vision was back to normal.

problem clinicians faced," Harris says. Spotting straightforward conditions had become much easier, and many of the cases presented at CPCs were now "zebras"—rare medical problems that few physicians would ever see. Harris announced that Case Records would strike into new territory—adding complex diseases where a patient history could help show other physicians new treatments or approaches to care.

These days, Rosenberg and his five deputy editors meet once a week to choose a case. Some ideas come unsolicited from MGH doctors, and Rosenberg occasionally requests suggestions based on a hot topic—such as the first patient admitted with H1N1 influenza in 2009. Exploring new territory in that way can be particularly valuable, and in 2020, 10 Case Records focused on patients with COVID-19. "Amid the chaos of the early days of the pandemic, Case Records provided a powerful way to share our experiences," says Rosenberg. Physicians from around the world presented COVID-19 cases at MGH's virtual CPCs. In one of those, a transplant nephrologist from Italy related how he was managing immunocompromised organ-transplant patients who got COVID-19. "Italy was a few weeks ahead of Boston in dealing with COVID, and we learned critical information about the patients we were just beginning to see," says Rosenberg.

One of the most widely read Case Records, published in 2010, involved the surgeon who operated on the wrong site and did the wrong procedure—and who courageously presented the case himself. "That allowed us to bring up the topic of physician errors, a topic Cabot had raised in the earliest days," says Rosenberg. "This was a phenomenally skilled surgeon, and if he could make that kind of error, there's a very good chance similar things are happening elsewhere." After explaining what went wrong, the surgeon also described new safety protocols put in place after his error.

During a CPC, presenters take the audience through the steps—and missteps—they considered in arriving at the likely diagnosis and conclude by stating what they think is wrong with the patient, as well as the test or procedure they would use to confirm the diagnosis. The pathologist who interpreted the patient's biopsy or the radiologist who read the definitive MRI or CT scan then gives the real diagnosis.

In one rare instance, there was no diagnosis. MGH hematologist David Sykes presented a patient with an unusual constellation of clinical conditions, including an excess of red blood cells and acute kidney failure. It was something he'd never seen before, and when the case was published online, Sykes asked readers to contact him if they had treated a similar patient. "Almost instantly, physicians from two other academic centers around the world responded with stories of patients just like the one David described," says Rosenberg. Discussing their patients, the clinicians realized they had discovered a new and ultra-rare disease which they called the TEMPI syndrome. In the 10 years since the CPC was published, Sykes and colleagues have identified 34 people worldwide with TEMPI syndrome and have published several papers on its diagnosis and treatment.

Case Records continues to evolve. For the past five years, for instance, Rosenberg has run an online quiz called Case Challenge, inviting *NEJM* readers to make a diagnosis using the same patient information that an upcoming case will be based on. Readers get to choose from among six possible diagnoses, and once they enter their answer, they can see how other readers have voted. Then, a week later, they can read that record to find out whether they were right or to learn why they were wrong. "Thousands of readers participate," says Rosenberg, who envisions other ways to make Case Records more multimedia and interactive, "especially for younger doctors who have never actually held a paper copy of *NEJM*."

While the formats may change and the platforms shift, Rosenberg sees the Case Records serving a central mission in medical education, one that will always be needed. "The case method takes unusual and fascinating medical cases, and it cleverly uses those to teach fundamental diagnostic and management skills," he says. "Someone once told me that medical school teaches you to think like a scientist," adds Harris, "but Case Records teaches you to think like a doctor."

IN ONE RARE INSTANCE, THERE WAS NO DIAGNOSIS.

The Case of Too Much Licorice

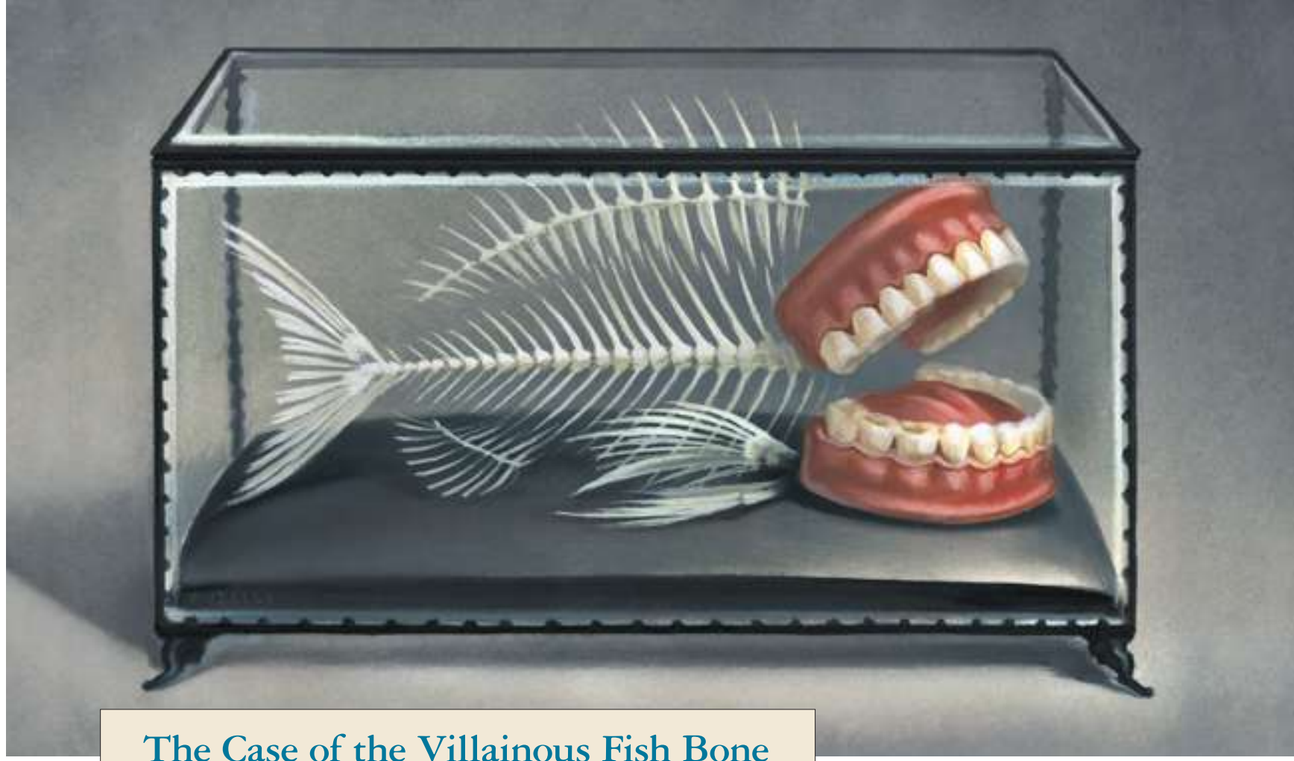
A man arrives at the emergency room after heart failure. Attention turns to his diet.

The 54-year-old collapsed in a fast-food restaurant, and it took a combination of injections, intravenous medications and electrical shocks to restart his heart. By the time he arrived at MGH, his heart rate was rapid and irregular, and his blood pressure was high.

Lab results showed a severe shortage of blood potassium, vital for proper heart functioning. The patient had no personal or family history of cardiac symptoms but had previously used heroin and had an untreated hepatitis C infection. Further tests, which ruled out other causes, led physicians to suspect that his low potassium levels were the result of a drug or food.

According to family members, the man subsisted on several bags of candy every day, and three weeks earlier had switched to licorice, an excess of which can cause heart problems.

As his organs shut down, the patient produced less and less urine, and his family declined further treatment. He died 32 hours after he arrived.



The Case of the Villainous Fish Bone

Symptoms compatible with infectious disease turn out to be the result of a meal gone wrong.

A 37-year-old New England expat, living in Vietnam, had experienced "rolling spasms" in his chest and, later, fevers, chills and body aches. Tests were negative for dengue, malaria, HIV and other diseases; an ultrasound showed a slightly enlarged liver and spleen. Further tests revealed bacteria in the blood and a CT scan showed possible lesions in the liver. A consulting MGH physician suspected a liver abscess—and the mortality rate for those may be as high as 12%. He urged transfer to MGH, where CT images revealed a "hyperdense" foreign body in the pancreas—a fish bone. Reaching the bone risked damaging vital organs, but a surgeon managed to get in, cut the bone in two and safely extract both pieces.

DOSSIER

"SARS-CoV-2: The Pandemic of Covid-19," Case Records of the Massachusetts General Hospital, May-September 2020, editors Eric S. Rosenberg and David N. Louis. The book is a collection of case studies of 10 COVID-19 patients with a range of ages and other illnesses. All of the cases were published in *The New England Journal of Medicine* and hold lessons about treating a novel illness.

***Keen Minds to Explore the Dark Continents of Disease*, edited by David N. Louis and Robert H. Young, January 2011.** This history of pathology at Massachusetts General Hospital devotes a chapter to the origin and development of Case Records, which have played a role in educating both young doctors and the wider profession.

A DISEASE OF BODY AND MIND

Once regarded as a purely mental condition, functional neurological disorder emerges from the shadows.

BY GABRIEL BROWNSTEIN //
PHOTO ILLUSTRATIONS BY
SUSANA BLASCO

One Sunday morning in January 2018, Eric McLaughlin was putting on his shoes while helping his son get ready for hockey practice. Suddenly, he felt he'd been "turned off," McLaughlin says, and when his wife asked him what was wrong, he found he couldn't speak. At the skating rink, the attacks of paralysis continued and became more intense. When parents of other kids approached, McLaughlin could hear them but was unable to respond.

At the time, McLaughlin's job was doing road maintenance in southern New Hampshire. He had never before had any physical or mental health problems that seemed serious. He had injured his ankle at a worksite, he suffered periodic migraines and some people described him as anxious—"I hate that word," McLaughlin says—but generally he was fine.

His primary care physician sent him to the local hospital, and he was admitted with a racing heart and monitored for cardiac arrhythmia. Yet the doctors found no clear reason for what he was experiencing. They described his condition as "mental," his racing heart as "psychosomatic." After McLaughlin was discharged, his doctor referred him to the Massachusetts General Hospital Emergency Department, where his inpatient team of physicians cataloged the symptoms: the tensing up, an increase in heart rate, confusion, sudden episodes of paralysis and his sense of a "fat tongue." Everything in his nervous system appeared to be structurally sound, yet it was nevertheless malfunctioning. Impulses in his brain were somehow being diverted or hijacked by certain neural pathways, causing seizures—so-called functional (psychogenic, non-epileptic) seizures—and other symptoms. They were the hallmark of a condition now known as functional neurological disorder, or FND.

FND, under various names, has perplexed physicians since ancient times. Many know it as conversion disorder, a term still in use, which frames the condition as a psychological illness—stress or neurosis expressed, or converted, into physical symptoms. But patients with FND aren't, by conventional standards, necessarily mentally ill, although many also suffer from anxiety, depression or post-traumatic stress disorder. Nor are these patients necessarily physically ill, though functional neurological symptoms may be observed in patients with strokes, epilepsy or Parkinson's disease.

Until very recently, FND remained largely mysterious. It wasn't a "rule in" diagnosis, something that test results might reliably point to. Often, in its many guises, it mimicked better known conditions. It was frequently a last resort, a diagnosis based on medically unexplained symptoms, arrived at only after ruling *out* everything else.

That confusion about the diagnosis and causes of FND has long been accompanied by a reluctance by physicians in various specialties to treat it. As recently as a few decades ago, and for a half century before that, neurologists had argued that symptoms such as those now associated with FND weren't real—the problems were entirely mental, performative, "all in your head." But while these patients may be more likely to have psychological trauma in their backgrounds, not all of them do, and the idea that this is the root cause of the disease is drastically changing.

With his diagnosis of FND, McLaughlin was referred to David Perez, a neurologist and psychiatrist who leads the Functional Neurological Disorder Unit at MGH. Perez is part of a pioneering international group of scientists who, helped by increasing sophistication in brain-scanning technology and other diagnostic tools, are beginning to solve the mystery of FND. Perez can help McLaughlin and patients like him with an expanding range of treatments that bridge the gap between neurology and psychiatry—a therapeutic approach which, like the disease itself, exists "at the intersection of the mind and brain."

• • • •

Since the beginning of medical history, physicians have recorded symptoms such as McLaughlin's—falling into seizures; losing the ability to stand, walk, talk, hear or see; or becoming paralyzed, all without apparent connections to muscles or the nervous system. In early Greek medical texts, such dysfunction was pinned on reproductive organs—a "wandering womb"—and it was then that the notion of "hysteria," from the Greek word for uterus, first became attached to the condition. (The historic connection to women persists, and today, about two or three times as many women as men are affected by FND.) In later eras, demonic possession was blamed. Although there was progress in diagnosing similar neurological conditions such as epilepsy and Parkinson's disease that had more visible organic symptoms, these cases continued to be mysterious. In the late 19th century, Pierre Janet, an influential French psychologist, physician and hypnotist, characterized functional neurologic symptoms as a matter of "suggestion," a too strong idea that overcame the patient. Jean-Martin Charcot, Janet's teacher and the father of modern neurology, looked for "dynamic lesions" in the brains of his patients that might be the source of these inexplicable breakdowns.

In the early 20th century, Sigmund Freud—who explored the phenomenon with physician Josef Breuer in his 1895 book *Studies on Hysteria*—argued that these conditions resulted from repression and were a physical expression of unspeakable traumatic memories. In his view, patients who were unable to name their emotional pain found their bodies involuntarily signaling it. Treatment, in his view, would come from psychoanalysis that could help identify patients' hidden trauma.

But the rise of the Freudian paradigm was accompanied by a loss of interest among neurologists. In 1908, prominent New York neurologist Bernard Sachs wrote that "while hysterical patients ... are numerous enough," their suffering was "less important than the sufferings of those afflicted with various forms of organic spinal disease." Soon, psychiatrists, too, backed away from the problem, which turned out not to be easily resolved with drugs or traditional psychoanalysis. In the mid-1960s, the book *Hysteria: The History of a Disease* announced "the near total disappearance" of hysteria as a diagnosis. In 1965, eminent British neurologist and psychiatrist Eliot Slater went further, arguing in a seminal paper that hysteria had never existed, but rather was the result of misdiagnosis. In the 1980s and 1990s, most doctors wanted little to do with these patients—who had become "almost literally invisible to medicine," according to historian Andrew Scull, who called them "modern medicine's untouchables."

Yet the years wore on, and their numbers could not be ignored. With clearer statistics, it became evident that FND touches about as many people as Parkinson's disease or multiple sclerosis. Functional neurological symptoms are the second most common reason for outpatient visits to neurology clinics. A turning point in acknowledging the condition came in 2000, when Sean A. Spence of the University of Sheffield in England published a study in *The Lancet*. Using positron emission tomography, Spence found distinctly different patterns of activation in the brains of diagnosed conversion patients compared with the brains of a control group—in this case, actors hired to feign the same symptoms.

Then in 2007, Jon Stone—a neurologist at the Centre for Clinical Brain Sciences at the University of Edinburgh and one of the leading global voices in FND diagnosis and treatment—published an article in which he and his colleagues built on Spence's results. Through MRI scans, Stone and his team looked at patients with functional ankle and leg weakness and discovered unusual patterns in several brain regions, involving the basal ganglia, insula, lingual gyri and inferior frontal cortex. Those brain patterns differed from those in people who faked the same conditions and suggested that motor control in the brains of people with FND might be somehow impaired.

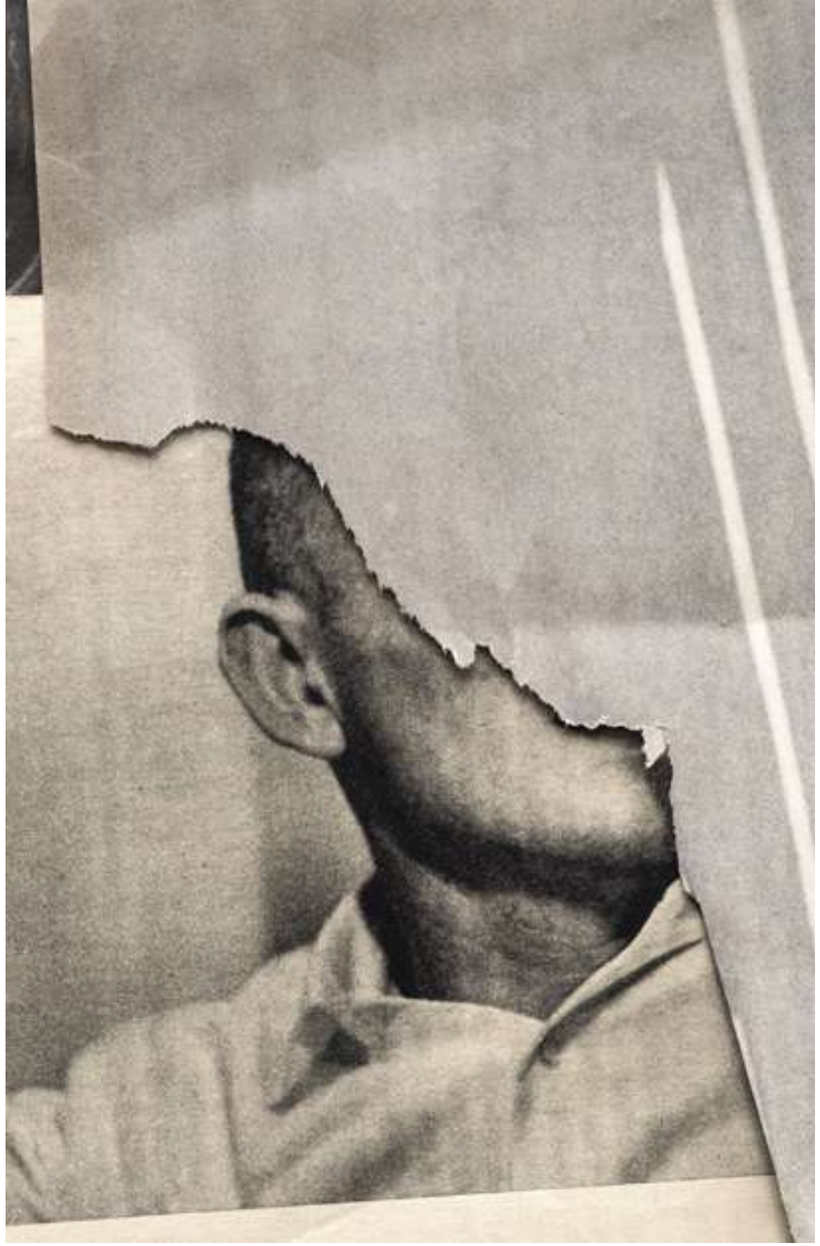
Later research brought this into clearer focus, revealing abnormal functional connections in certain brain networks. For example, irregularities appeared in the salience network—a collection of neurons in the cortical and subcortical parts of the brain that help process and determine the relevance of sensory information—and the limbic network, the deep brain connections involved in emotion processing. In a 2010 study published in *Neurology*, Valerie Voon, a neuropsychiatrist at the University of Cambridge, suggested that people with FND have reduced activity at the right temporal parietal junction, a crucial node in the network that controls self-agency, or the sense people have of directing their own bodies.

One idea to come out of this research is that, for people with FND, unusual interactions between brain networks—between prediction and response—lead to impairments in feedback and feed-forward loops. These may make it difficult to perceive or predict threats or to respond to them. So Eric McLaughlin felt perfectly calm while his heart raced and his limbs froze.

• • • •

Today the condition straddles two terms in the DSM-5, the chief taxonomic tool of the American Psychiatric Association. Conversion disorder remains on the books, albeit in a secondary position to functional neurological disorder. The latter is a newer and overlapping description of nearly identical symptoms. It is the result of an effort by Stone and colleagues to correct the judgment implied by "conversion disorder" and the term's connection with the older ideas of hysterical conversion, which posits a singular cause almost entirely within the mind. The new model proposed by Stone, Perez and others suggests a "biopsychosocial" origin—a problem with multiple roots in brain biology, patient history and the social context of their lives.

In his work, David Perez brings all of these factors together. In addition to leading the FND Unit at MGH, Perez is director of the MGH Functional Neurological Disorder Research Group, and for much of the past decade he has published extensively on FND, leaning into his training as a psychiatrist, neurologist and neuroscientist. The pressure to distinguish too neatly between physical and mental health in FND may not be necessary. "Some patients with FND that I encounter may have important psychological disturbances," he says, "yet when they have



trouble walking or have convulsions, their symptoms are every bit as real, and every bit as brain-based, as those of patients with stroke or Parkinson's disease."

Some of those symptoms—seizures that aren't easily explained by electrical storms in the brain (functional seizures) and difficulty in controlling movements (functional movement disorder, or FMD)—have been at the heart of his research. In terms of sheer numbers, these two conditions represent a crisis in neurology. "In epilepsy and movement disorder subspecialties, upwards of 20% to 30% of patients admitted to the epilepsy monitoring units and 20% of patients seen in movement disorder clinics" have functional seizures or FMD, he wrote in a 2015 paper. Yet despite the frequency with which neurologists encounter these conditions, most have "limited comfort" in caring for them.

Perez notes that in more recent years, research has started to settle into a working model of how the condition probably takes shape in the brain. In a 2021 review article that focuses on functional motor symptoms, Perez and his co-authors outline possible mechanisms. When people need to make voluntary movements, the brain switches between consciously experiencing control of movement and the neural networks that perceive those movements and enable them to occur. Problems like speechlessness or paralysis may arise when nonconscious cognitive, perceptual and affective processes interfere with the sensory and motor parts of the process.

Sometimes that kind of problem may develop after an injury, Perez says. Focusing on what has been hurt—Eric McLaughlin thinking about his injured ankle, for example—could bring "heightened attention to the self and activation of bodily arousal systems." An important implication of this and other recent work has been to support the idea that FND is a brain-based condition that bridges neurology and psychiatry, Perez says.

Indeed, as a wealth of research shows, FND can't be understood exclusively as the result of either psychological or biological factors. For Freud, conversion disorders began in childhood trauma, with episodes of hysterical conversion happening when the memory was summoned and repressed. Experts in the field note that between 20% and 50% of patients with functional seizures have experienced sexual or physical abuse or neglect—but while traumatic childhood experiences can be seen as a risk factor, they are not a clear-cut cause.

Events during childhood can affect brain development, sometimes leading to over-activation of parts of the limbic system, including the amygdala and the hippocampus. And a study published in *Epilepsy & Behavior* in September 2021 explored one way in which such psychological factors might manifest themselves to promote functional seizures. The study compared fMRI brain scans of 23 people having functional seizures to 25 healthy controls. Noting the differences in several brain areas, the researchers concluded that emotion-processing regions in the patients experiencing the seizures inhibited the brain's executive control areas and motor regions. That suggests emotional arousal could contribute to the problem, and that cognitive behavioral therapy might help those patients regulate their emotions and avoid seizures.

Social and cultural factors can play a role, too. In a 2021 article in *JAMA Neurology*, Perez and several colleagues noted that some adverse responses to the COVID-19 vaccine, such as seizures and abnormal movements, are "seemingly consistent with FND." The patients aren't faking their symptoms, yet it's unlikely the chemistry of the vaccines plays a causative role in FND—a shot of saline water might have the same effect.

• • • •

When Perez established his FND clinic at MGH in 2014, it was embedded across the neurology and psychiatry departments. It has since been elevated to its own unit, and its growing multidisciplinary and interdisciplinary staff includes five neurologists and two psychiatrists, as well as a speech therapist, a physical therapist, an occupational therapist and two psychotherapists.

New patients meet a physician for a 90-minute assessment and work collaboratively to put together a plan of action that can run the gamut—a personalized combination of talk therapy, speech therapy, physical therapy and occupational therapy. "One patient may have never seen a psychiatrist," says Perez. "Another may have been psychiatrically hospitalized multiple times with a range of active mood-, anxiety- and trauma-related symptoms." Even two patients with nearly identical physical symptoms may have divergent treatment needs. In working with his patients, Perez and his team look not only to understand the complex biopsychosocial factors contributing to disabilities but also to explain them in a way that promotes growth and recovery.

A PLAN OF ACTION FOR TREATMENT CAN RUN THE GAMUT—TALK THERAPY, SPEECH THERAPY, PHYSICAL THERAPY AND OCCUPATIONAL THERAPY.

Kyla Kenney, a singer from Rhode Island, went to the FND Unit because she was experiencing crippling headaches and tremors. Other doctors had found no reasons for her condition. But Perez showed her that the likely diagnosis of FND meant that she was experiencing a common, diagnosable disorder that could be treated. He prescribed a combination of cognitive behavioral therapy and occupational therapy, and through that, she has learned a set of skills to help with her tremors. She keeps super sour candies (a "sensory snack") in her purse, and when she feels symptoms coming on, she pops one in her mouth—the awful taste can distract her and prevent tremors.

Meanwhile, Perez and his colleagues are contributing to a renewed scientific interest in FND. He recently received a $4.1 million grant from the National Institutes of Health to use fMRI imaging to better understand the brain network mechanisms underlying symptoms, disease risk and clinical outcomes. Separate, recently published work by another group explores the possible impact of stress-related systemic low-grade inflammation on patients with FND. The researchers discovered elevated levels of inflammation in patients with FND that could possibly mimic stroke-like symptoms, and microRNA levels in the blood also seemed to play a role, influencing the expression of genes.

One major advance Perez hopes to see in the next few years is the stigma of FND finally falling away—not only among the public but his colleagues across the clinical brain sciences. "For decades, these have been patients that we couldn't help much, and so many of them were told that their disease was all in their minds," he says. "But our job is to be doctors of the brain *and* mind. The science is finally catching up. And as the picture becomes clearer, we have so many people that we can help."

DOSSIER

"Decade of progress in motor functional neurological disorder: continuing the momentum," by David L. Perez et al., *Journal of Neurology, Neurosurgery & Psychiatry*, March 2021. The article reviews the past decade of progress in FND in the areas of diagnosis, mechanisms and treatments. The paper also explores the ongoing stigma within both the health care and outside communities around FND and what the next decade may bring.

***Hysteria: The History of a Disease*, by Ilza Veith, University of Chicago Press, 1965.** Despite the importance of hysteria to Sigmund Freud and other founders of psychology, little had been written about the condition he seemed to describe and the evolution of its understanding across time. This book fills that gap until the 1960s, a time when actual diagnoses of hysteria had dropped off.

FIRST PERSON

Yes, Mother

BY CARI SHANE

"Did you speak to Alan?"

my mother asks.

"You mean Dr. Alan, your dentist?"

"No. No. Alan! The man I'm dating," she says, a smile forming on her 92-year-old face. My mother is lying in bed, layers of blankets covering her 80-pound frame. I cover her toes with one of the blankets as she continues to tell me about her new romance. Today, her voice sounds firmer, more lucid, like the woman I used to know, the fierce woman with the smarts and charm of a young Suzanne Pleshette.

I miss this mother, the woman who seemed to fear nothing. In her day, she'd studied Shakespeare, climbed the corporate ladder and taught me how to be an ardent feminist, speaking my truth. But now, as she talks about this man, truth is a trickier topic. Alan can't possibly be real.

"And where did you meet Alan?" I ask.

"I met him at the club I joined," she says. "It was so odd, I met him that first night, and Aunt Marion was there, too." My mother's brow furrows. "It is strange, though, because I know my sister died 10 years ago."

It has taken me some time to get used to the mental turns that her dementia takes. One of the biggest battles had been the dog. "She thinks she has a dog," I told the geriatrician. "Only no one else can see him." My mother had instructed the aides to put down a water dish, and soon after, dog food. It was innocent enough until one day she grew livid, hitting herself, when the aides refused to make a vet appointment.

We saw a neurologist who diagnosed Lewy body disease, a progressive form of dementia that often comes with hallucinations and mood changes. When she heard the diagnosis, my mother confessed that she'd been living with demons, horrible, scary, disfigured people who told her what to do. Those visions left her confused and anxious. Medications were prescribed, but a few weeks in, it was clear they weren't helping.

When the hallucinations first became part of her daily reality, I tried to reason them out of her during my visits. I tried changing the topic. I always left defeated, a flattened bulwark against the tide of her demons.

The neurologist had a suggestion: relax my need for her to face facts. Learn how to lie.

"My mother is the woman who taught me not to lie," I said. "I don't feel comfortable with that."

The more I struggled, though, the more I considered it. I read the literature he suggested. The Alzheimer's Association laid out a few medical theories, including "therapeutic fibbing" and "loving deception," both ways to approach patients who can't make sense of the truth. Other experts championed an approach called the "validation method," which focuses not on getting caught up in the facts as I had been doing, but instead trying to connect and understand the world in which the dementia patient lives.

They all agree on one thing: There is a moral difference between lying for your own gain and lying to protect and care for someone else. And it seemed to me that joining in my mother's lie—some of them at least—might be the way to keep her calm and maybe even sometimes make her happy.

Over the next months I learned to combine these three methods. I trained my mother's aides to use them, too. We learned when to let her lead the way, and slowly things got more peaceful.

Today, I tell her that Alan sounds charming. She asks me about the phone call I had with him. I'm taken aback only for a moment, then I take a breath and tell her that he really likes her, he told me so himself.

She smiles. I realize this conversation that would have made my heart sink a month ago is doing something different—making us both feel calm and loved. And for now, that's all I need.

COLLAGED IMAGES FROM GETTY IMAGES

Massachusetts General Hospital
55 Fruit Street
Boston, MA 02114

The Future Is Here

Innovation moves quickly in the field of medicine. **Follow** *Proto* to explore those frontiers as they emerge.

Sign up for the print magazine and newsletter at ProtoMag.com.

Subscribe to the *Proto* podcast on iTunes and Stitcher.

ProtoMag.com
@ProtoMagazine
Facebook.com/ProtoMag
Proto.Magazine